FEEDBACK PROCESSING IN SENSORIMOTOR TRANSFORMATION TASKS

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I Summary

Purposeful motor actions are based on the analysis of sensory information and on the planning and execution of motor programs. The processes of converting external information into motor commands can be summarized as “sensorimotor transformation”. The assessment of the consequence of an action is an important factor in the assessment of whether the action has led to the required result. For example, if a man wants to switch off a light, his first step will be to look for the light switch. The second step will be to plan and execute the motor action, taking the position of the hand and the light switch into account. The third step will be to check – again by sensory means – whether the light really has gone off. If so, the action has been successful.

The main focus of this dissertation lies in the processing of *feedback* as part of sensorimotor transformations. We investigated various types of feedback. All three studies in this dissertation used functional magnetic resonance imaging (fMRI) measurements of sensorimotor transformation tasks.

The first study addressed the question of how brain activity is affected by the *properties of the visual stimulus* on the one hand, and by the *type of action* into which the visual information needs to be converted on the other. The results show that analysis of spatial information in visual stimuli activates the inferior parietal cortex when contrasted with visual stimuli that do not contain any spatial information (e.g. colours). This result fits nicely with the existing literature, which assumes that the analysis of spatial information occurs in the dorsal pathway through the parietal cortex. Differences also exist on the level of dynamic and isometric movement: Dynamic movements, i.e. movements that require the hand to be displaced in a spatial dimension, demonstrate stronger and more extended activation in the fronto-parietal cortex than isometric, static movements. The more extensive fronto-parietal activation for dynamic movements can be traced to the activation of various muscle groups that make it possible for the finger to carry out a gripping movement and for the hand to be displaced. It appears that the type of movement is more important than the type of visual stimulus for the activation in the parietal cortex.

The aim of the second study was to investigate brain activity related to various forms of failure. The example above can be modified to illustrate this well. If the light goes off after the switch has been operated, the action has fulfilled its goal. However, if the

light does not go off, there might be different reasons for this failure. On the one hand, the action may not have been carried out adequately. On the other hand, it might be due to a faulty light switch. Depending on the source of the failure different consequences need to be taken. If the fault is an error of the *person* carrying out the action, it is important that his internal model, which planned and predicted the movements, should be optimized. However, if the cause is out of control of the person carrying out the action, a change in the internal model will make no difference. Our experiment shows that internal errors, i.e. those that have been caused by the person carrying out the action, are coded differently from those that are caused by faults in the environment (e.g. a faulty light switch). This can provide the neural basis for different consequences depending on the source of error. If the person carries out an action inadequately, it is important that the internal model used to plan the movement is made aware of this error, and that the planning for the movement is optimised.

The third study investigates the neuronal correlates of positive feedback and of positive feedback that is coupled to a monetary reward. We compared brain activity when subjects received feedback for correct performance with the brain activity when subjects received a cash reward along with the positive feedback. From a functional point of view, the striatum is one of the most important structures in the processing of cash rewards and positive feedback. The results demonstrate that the activation of the dorsal and ventral striatum differs between the two conditions. The ventral striatum is more activated by positive feedback (in contrast to negative feedback), independently of whether the person has received a cash reward or not. In contrast, dorsal striatal activity is only increased when the positive feedback is presented in combination with a monetary reward.

Taken together, the aim of this thesis was to shed light on three different facets of feedback. We showed that different areas were activated, depending on the importance and meaning of the feedback – even though the same sensorimotor transformation task was involved three times in this study. This suggests that various types of information provided by the feedback are analyzed by specialized areas in each case. In other words: Feedback is not a unitary construct. The neural processing of feedback is strongly modulated by the specific source of information. This differentiated view provides an important basis for future work on neural coding of feedback.

II Zusammenfassung

Zielgerichtete motorische Handlungen basieren auf der Analyse sensorischer Informationen und, unter Berücksichtigung ebendieser, der Planung und Ausführung der motorischen Programme. Die Prozesse, welche externe Information in motorische Befehle umwandeln, werden unter dem Begriff *sensomotorische Transformationen* zusammengefasst. Wichtig für die Beurteilung, ob die Handlung zum gewünschten Ergebnis geführt hat, ist die Bewertung der Konsequenz der Handlung. Will man z. B. das Licht löschen, wird in einem ersten Schritt nachgeschaut, wo sich der Lichtschalter befindet, in einem zweiten wird unter Einbeziehung der Position der Hand und des Lichtschalters die motorische Handlung geplant und ausgeführt. In einem dritten Schritt wird überprüft – wieder auf sensorischem Weg – ob das Licht wirklich ausgeschaltet ist. Ist dies der Fall, war die Handlung erfolgreich.

Der Hauptfokus der vorliegenden Dissertation liegt in der Verarbeitung von Rückmeldungen im Rahmen sensomotorischer Transformationsaufgaben. Wir untersuchten drei Facetten von Rückmeldung. Die Rückmeldungen können sich unterscheiden, z. B. hinsichtlich ihrer Form, ihrer Erwartungsübereinstimmung oder persönlicher Bedeutung. Alle drei Studien dieser Dissertation wurden mit der funktionellen Magnetresonanztomographie gemessen und basieren auf einer sensomotorischen Transformationsaufgabe.

Die erste Studie beschäftigt sich mit der Frage, wie die Gehirnaktivität einerseits durch die Eigenschaften der visuellen Reize, andererseits durch die Handlungsart, in welche die visuelle Information übersetzt werden müssen, beeinflusst wird. Die Resultate zeigen, dass die Analyse von visuellen Reizen, die räumliche Informationen erhalten, im Gegensatz zu visuellen Reizen, die keine räumliche Information beinhalten (z.B. Farben), zusätzlich den inferioren parietalen Kortex aktivieren. Dieses Resultat lässt sich gut in die bestehende Literatur einbetten, die dem dorsalen Pfad, der durch den parietalen Kortex zieht, die Analyse räumlicher Informationen zuschreibt. Auch auf der Bewegungsebene finden sich Unterschiede: dynamische Bewegungen, d.h. Bewegungen, die eine Verschiebung der Hand in einer räumlichen Dimension verlangen, zeigen verstärkte und grossflächigere Aktivierungen im fronto-parietalen Kortex, als isometrische, statische Bewegungen. Die verstärkte fronto-parietale Ausdehnung bei dynamischen Bewegungen scheint auf die Aktivierung verschiedener Muskelgruppen zurückgeführt werden zu können,

die die Greifbewegung der Finger und das Verschieben der Hand erst ermöglichen. Es scheint, als würde die Aktivierung im parietalen Kortex stärker durch die die Art der Bewegung als die Art des visuellen Reizes beeinflusst zu sein..

Das Ziel der zweiten Studie war es, die Gehirnaktivität, die mit verschiedenen Fehlerarten und deren Grösse korreliert, zu untersuchen. Anhand des Eingangsbeispieles lässt sich die zweite Fragestellung gut darstellen. Ist nach dem Betätigen des Schalters das Licht aus, so führte die Handlung zum Ziel; ist dies jedoch nicht der Fall, kann dies verschiedene Ursachen haben. Einerseits kann z.B. die Handlung nicht adäquat ausgeführt worden sein, andererseits kann ein solches Ergebnis auch durch einen defekten Lichtschalter zustande gekommen sein. Je nach Fehlerquelle werden andere Lösungen gebraucht. Liegt der Fehler innerhalb des Handelnden, so ist es wichtig, dass dessen internales Modell, das die Bewegungen plant und vorhersagt, optimiert wird. Liegt die Quelle ausserhalb des Handelnden, bringt eine solche Änderung des internales Modells nichts. Die Resultate dieses Experimentes zeigen auf, dass interne Fehler, d.h. solche, die von der handelnden Person gemacht werden, anders kodiert werden, als Fehler, die durch die Umgebung (defekter Lichtschalter) bedingt sind. Führt eine Person eine Handlung inadäquat aus, so ist es wichtig, dass das interne Modell, das die Bewegung plant, auf diese Fehler aufmerksam gemacht, und die Bewegungsplanung optimiert wird.

Die dritte Studie untersucht die neuronalen Korrelate positiver Rückmeldung und positiver Rückmeldung, die an eine monetäre Belohung gekoppelt ist. Wir verglichen die Hirnaktivität während positiver Rückmeldung mit und ohne zusätzlicher monetärer Belohnung. Funktional gesehen, ist das Striatum eine der wichtigsten Strukturen, die monetäre Belohnung und positive Rückmeldung verarbeitet. Unsere Resultate zeigen, dass sich die Aktivierungsweise der beiden Bedingungen fundamental voneinander unterscheiden. Das ventrale Striatum ist stärker aktiviert, wenn es sich um eine positive Rückmeldung im Gegensatz zu einer negativen Rückmeldung handelt, wobei die monetäre Belohnung noch eine zusätzliche Aktivierung mit sich bringt. Die dorsale Aktivität hingegen ist nur erhöht, wenn die positive Rückmeldung mit Geld bedacht ist.

Das Ziel der Arbeit war es, drei verschiedene Facetten der Rückmeldung zu beleuchten. Es konnte gezeigt werden, dass – obwohl es sich drei Mal um eine sensomotorische Transformationsaufgabe handelte – je nach der Wichtigkeit und Bedeutung der Rückmeldung, unterschiedliche Areale aktiviert werden. D.h. dass die

unterschiedliche Information, die in der Rückmeldung beinhaltet sind, von den jeweils spezialisierten Arealen analysiert werden. In anderen Worten, Rückmeldungsverarbeitung ist nicht ein einheitliches Konstrukt. Die Rückmeldungsverarbeitung wird stark durch die Inhalte der Rückmeldung moduliert. Diese differenzierte Sicht liefert eine wichtige Basis für weitere Arbeiten, die sich mit den neuronalen Korrelaten von Rückmeldung beschäftigen.

1. Introduction

In our every day life, the consequences of most of our actions are fed back to us in some way. For example, when we turn a knob the light goes on, when we turn on the air conditioning cool air fills the room, when we press a button, the radio turns on. We are informed about the consequence of our actions via sensory feedback. Sensory feedback can stem from different sensory modalities, like vision, hearing, temperature, smell, or touch and can follow immediately after the action or with delay. Feedback, whatever form it takes, contains information about the outcome of an action. Once the feedback is registered by the agent, it is evaluated and consequences are taken. We learn that our action of turning on the radio was successful when we hear music. We learn about that our action of switching on the light was successful when the room is illuminated. But in some cases the consequences that are fed back to us may not correspond to what we expected. Imagine yourself turning on the heating system and a cool breeze is emitted. In this case you might get surprised, irritated or even angry since your expectation is violated. Most importantly, in many cases the cause of the failure might not be obvious. We might have simply made a mistake and pressed the wrong button, or the failure may be due to a broken air conditioning. Therefore, outcome failures of actions can reflect either errors made by the agent (e.g. their internal model might have been wrong) or by the environment (the broken air conditioning). Furthermore, feedback is not only evaluated with respect to its modality and expectedness, but also with respect to the reward that comes with it. A successfully solved task may not only lead to a positive feedback about performance, but it may also be linked to monetary gain or social respect. Thus, taken together, performance feedback can be evaluated with respect to its *modality* (e.g. cold/warmth), its *expectedness* (expected/unexpected) or its reward relatedness (e.g., primary/secondary, extrinsic/intrinsic).

The aim of this thesis was to investigate the different aspects of feedback processing. For this purpose we designed a scanner-compatible sensorimotor transformation task that is used in all three experiments. Sensorimotor transformations describe processes that rely on sensory information that induce or are taken into account for planning and executing a motor response. For example, when we want to switch on the light, we first look where the switch is located, grasp and move it and wait for the light to illuminate. We use visual information about the location of the switch and proprioceptive information about the location of the hand to

plan the movement and we are informed about the successful manipulation again via sensory information.

In our experiments, subjects had to apply a force on a force-grip device as indicated by the target cue (Fig. 1). In each trial, subjects were first shown the target position (yellow square). They were instructed to apply a force that matched the target position to the force-grip device immediately after target presentation. The force applied was translated into a position along the horizontal line. Feedback cues were always shown below the line in red. The spatial distance between the target and feedback cue was regarded as the motor error. The subjects' task was to perform this transformation as precise as possible. After presentation of the feedback, a written instruction was presented to remove force from the dynamometer and a new trial subsequently began.

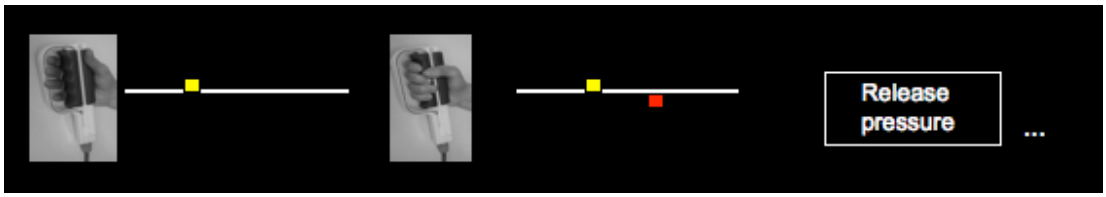


Fig. 1 Basic structure of the sensorimotor transformation task used in this thesis. Subjects were holding a force-grip device in their right hand. On a screen they were projected a white line with a yellow square on it. The horizontal position of the yellow square indicated the force to be applied to the force-grip device. The square's position was varied from trial to trial. Thus the required motor response changed from trial to trial. The red square is the feedback of the actual force applied. The difference between the two is the error. The aim was to be as precise a possible.

By varying the different components of the task we are able to investigate different aspects of feedback processing. A short overview about the three tasks used in this thesis is given below, a more detailed description follows in chapter 2.

Study 1: The first study deals with different feedback *modalities*. To this purpose two different sets of sensory cues and motor responses are used. The cue that indicates which force has to be applied can either be spatial (the horizontal position of the target square) or non-spatial (the color of the target square). Both, the position along the line, as well the color, indicate which motor response is required. Bright colors require only small force applications, while dark colors require higher force application. Yellow squares at the left side of the line, require small force application,

while yellow squares positioned on the right side of the line, require higher force application. Additionally to the sensory side, also on the response side the motor requirements were varied with respect to their spatial demands: the motor response once required a dynamic (limb coordination in space) and an isometric manipulation (no spatial coordination). For the isometric motor response a force-grip device (as shown in Fig. 1) was used, for the dynamic movement, an additional tool had to be be used.

Study 2: The second study investigates the neuronal processing of *correct* vs. *incorrect feedback*. For this purpose, we used the task as described in Fig. 1. In addition to correct feedback, in some trials the feedback about the subjects' performance was incorrect (an additional random error was added).

Study 3: The third study targets the differential processing of feedback in regard to its *performance level* and *monetary gain*. For this purpose, we added a monetary reward component that could be obtained for high performance in half of the trials.

As a prerequisite to the experimental work, the next three sections review neural processing of sensorimotor transformations and of feedback processing more closely. An introduction to the applied methods is given in chapter 3. In chapters 4, 5, and 6, the three empirical studies are presented in form of independent manuscripts. The last section summarizes the three empirical studies and discusses their implications and also their potential weaknesses with an outlook for future work.

2. Theoretical Background and Research Questions

2.1 Sensorimotor transformation and the variation of sensory and motor processes by spatial characteristics

The aim of the first study was to investigate the neural impact of transforming visual stimuli into motor responses. Two kinds of visual stimuli were used. One consisted of a dot along a line and contained spatial information. To correctly translate this square position into the required motor response a spatial judgment had to be done. The other visual stimuli consisted of a colored square. Each presented color tone was associated with a specific motor response. Such spatial information and shape information are known to be processed in different pathways. Also on the motor side, the responses were varied with respect to their spatial content. The dynamic motor response required a dislocation of the hand on the horizontal plane. The isometric movement required no such dislocation.

From an anatomical point of view visual information first reaches the retina and is projected to the primary and secondary visual areas in the occipital lobe (Fig. 2). From there it is further distributed to the temporal and parietal lobe. Ungerleider and Miskhin (1982) proposed a theory based on the distinction between dorsal (parietal lobe) and ventral (temporal lobe) pathways. This theory states that the dorsal pathway is responsible for extracting information about the *spatial* characteristics of the environment and about motion, while the ventral pathway extracts information about the *form, color, and identity* of objects.

In the early 90s Goodale and Milner (1992) proposed a slightly different view of the involvement of the ventral and dorsal pathway. They proposed that the dorsal visual stream (parietal lobe) registers visual information about the goal, transforms this information into appropriate coordinates and enables planning of skilled actions. They called their concept „*vision for action*“ (dorsal stream) in contrast to „*vision for perception*“, which is in turn enabled by the ventral stream.

Milner and Goodale’s concept of the dorsal stream has been challenged and modified over the past years. New anatomical data and the reassessment of clinical studies suggest that the dorsal stream should be divided into two substreams, namely a dorso-dorsal and a ventro-dorsal stream (Rizzolatti & Matelli, 2003).

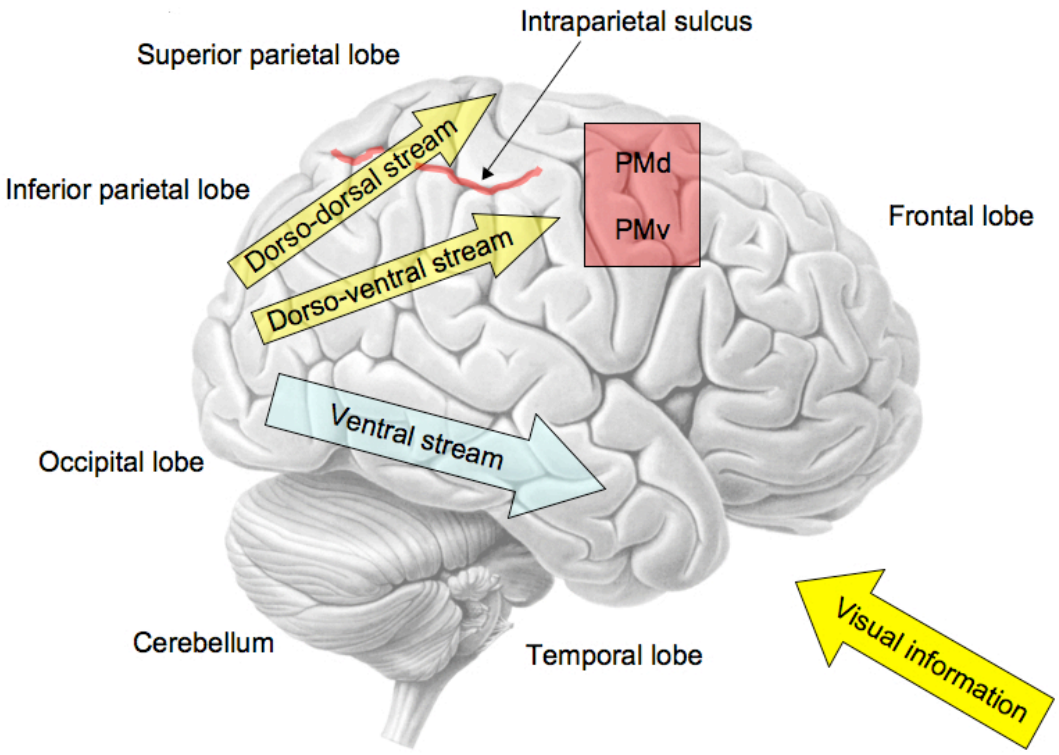


Fig. 2 View of the brain's surface. The yellow arrows on the top left indicate the dorsal pathway and its projections into the premotor cortex (subdivided into the dorso-dorso and dorso-ventral stream). The blue arrow illustrates the ventral stream.

It has been argued that the dorso-dorsal stream (superior posterior parietal lobe) is limited to the control of immediate visuo-motor control whereas the ventro-dorsal stream (inferior posterior parietal lobe) is involved in complex planning and programming of motor responses relying on higher representational levels (Pisella et al., 2006).

The parietal cortex and especially the intraparietal sulcus (IPS), which divides the parietal lobe into an inferior and superior lobule, has been proposed to act as an integration site for sensory information and motor control. Stark and Zohary (2008) report two opposite gradients in the IPS: The weighted involvement in the analysis of visual-field information decreases from anterior to posterior whereas the weight of the movement planning factor increases. From the parietal cortex information is then projected to the premotor areas, which are anatomically and functionally tightly linked with the parietal cortex (Tanne et al., 1995; Binkofski et al., 1999a; Grol et al., 2007; Blum et al., 2007; Blum et al., 2008). Thus, there is a two-fold involvement of the *dorsal stream*: On the one hand it performs an analysis of spatial information contained in stimuli as proposed by Unglerleider and Mishkin (1982) and on the other it performs an integration of visual information into motor responses. This raises the

question which impact these components (sensory information and motor parameters) have on parietal activity. This question formed the basis of our first experiment.

Research questions study 1:

Study 1 addresses three questions related to the role of parietal cortex in sensorimotor control:

I) How is brain activity influenced by visual instruction cues and feedback with and without spatial information?

II) How does the representation of movements in brain activity differ with and without the requirement for limb coordination in space?

III) How do these two aspects of sensorimotor integration interact with each other?

To address these questions a variant of the basic sensorimotor transformation task described earlier (Fig. 1) was used. On the one side the sensory information (target cue and feedback) was varied with respect to its spatial information and on the other side the motor action was varied with respect to spatial demands (Fig. 3). The stimulus containing spatial information was presented as a square positioned along a horizontal line. The square's position determines the required motor response. A spatial judgement had to be performed by the participant to plan the required motor response. The stimulus containing no spatial information consisted of a colored square with the color containing information about the required motor response. Additionally the motor response was varied: The first type of motor response consisted of displacing a lever in the horizontal line. This dynamic movement required limb coordination on the horizontal plane. The second type of movement consisted of applying pressure on a force-grip device. This isometric movement did not require any crucial limb movement in the horizontal or vertical plane.

In general, motor planning and online-monitoring as well as the analysis of spatial characteristics of visual stimuli have been located within the parietal areas (Toni et al., 2001b). The aim of this study was to distinguish the neural processing of these variables (motor-spatial versus sensory-spatial) in the parietal lobe.

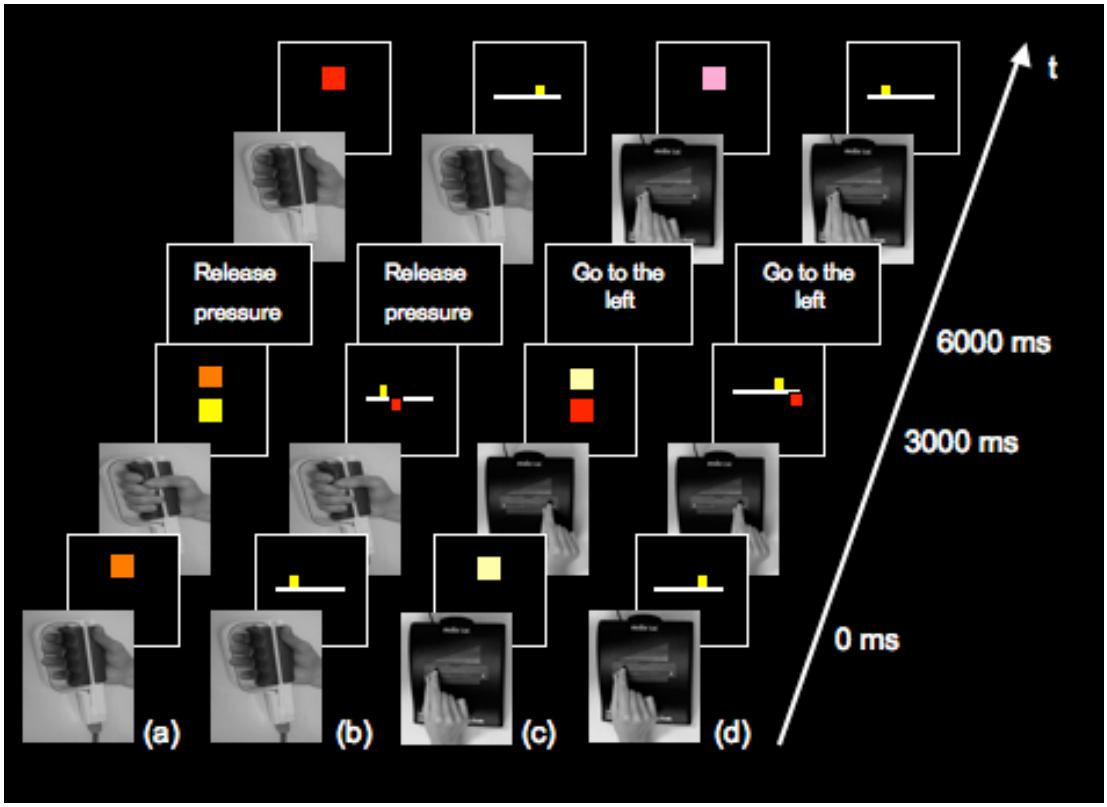


Fig. 3 The four task conditions are depicted from a-d. At time point 0, subjects were presented with a target (either a colored square or a dot above a horizontal line), upon which they had to manipulate the tool in their hand. After three seconds, they were given feedback about their performance, lasting for a further three seconds. At the end, subjects were instructed to release the pressure on the force-grip device or to reset the lever at the leftmost position. (a) The "isometric-movement/color" condition contained no spatial properties, neither on the sensory nor on the motor side. Pressure intensity required was represented by the color of the square. (b) The "isometric movement/dot-on-a-line" condition contained spatial aspects on the sensory side, but none on the motor side. (c) The "dynamic movement/color" condition contained spatial properties of the motor parameters, but none on the feedback. (d) The "dynamic movement/dot-on-a-line" condition contained spatial properties on both sides.

2.2 Sensorimotor transformation tasks and monitoring of expected and unexpected outcome

The aim of the first study was to investigate the neural activity linked to the integration of sensory stimuli into motor responses. The goal of the second study is shifted towards performance monitoring and error perception.

To be efficient in our everyday life, it is of great importance to verify the consequences of our motor actions by comparing the actual outcome with the intended outcome. Classical error monitoring has focused on cognitive rather than motor tasks. Typically, the tasks used are modified flanker tasks, in which subjects have to evaluate the presence or absence of a specific stimulus among distractors.

Performance monitoring research has mainly investigated self-generated internal errors (Ullsperger & von Cramon, 2003; Ullsperger & von Cramon, 2004; Fiehler et al., 2004; Mars et al., 2005; Ullsperger & von Cramon, 2006) with a few exceptions that focused on the neural activity of self generated versus externally induced errors (Ullsperger et al., 2007; Holroyd et al., 2001).

Functionally, cognitive error monitoring has consistently been linked to the pMFC (posterior medial frontal cortex) activity (Fig. 4). Anatomically the pMFC includes the median part of the superior frontal sulcus (BA 6, 8, 9, 10, 11), the supplementary and pre-supplementary motor areas (BA 6, 8) and the anterior cingulate cortex ACC (BA 24, 32) (Ridderinkhof et al., 2004).

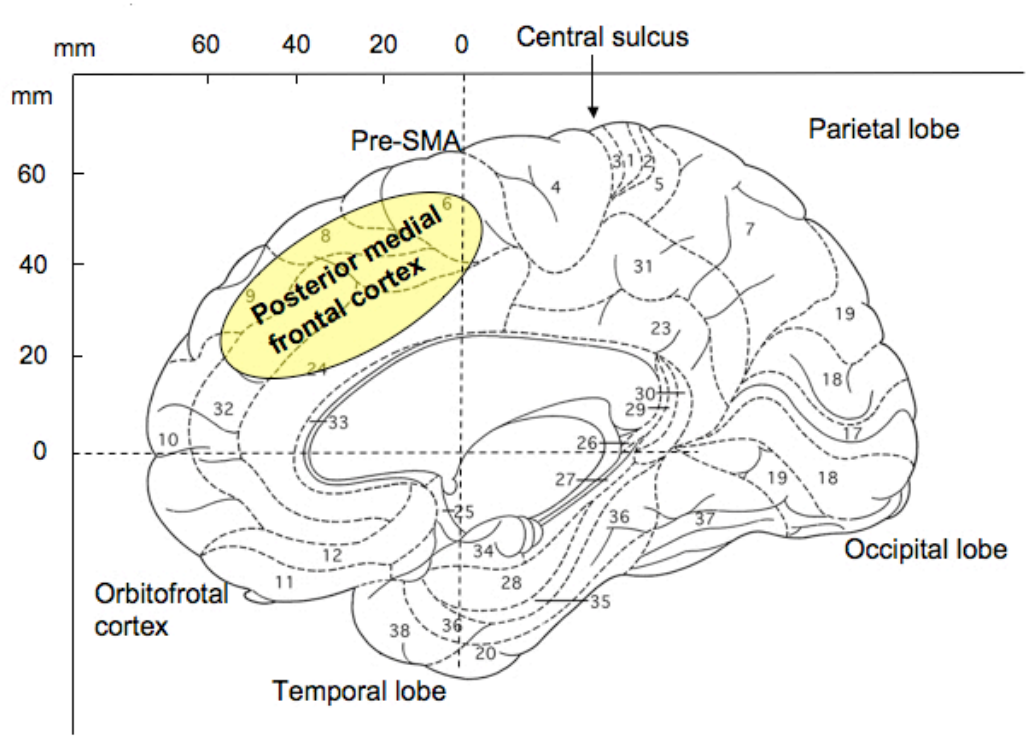


Fig. 4 Medial view of the brain. The yellow ellipse shows the posterior medial frontal cortex, a region frequently activated by cognitive error monitoring tasks.

Error perception and monitoring has not only been investigated with respect to the cognitive evaluation of a specific stimulus, but also with respect to the planning and execution of motor acts (Blakemore et al., 2001; Blakemore, 2003; Imamizu et al., 2003; Imamizu et al., 2004). It has been proposed that planning of motor responses are governed by internal models (Wolpert et al., 1995; Wolpert & Kawato, 1998). These internal models have been assumed to consist of two parts, an inverse and a

forward model (Fig. 5). The inverse model calculates the motor commands required to achieve a certain goal, while the forward model makes predictions about sensory consequences of motor commands. Deviations from the predicted sensory consequences and the actual outcome can be detected by the forward model and used to update motor commands or to adapt the internal model. The internal models have been proposed to be located in the parietal lobe and the cerebellum (Imamizu et al., 2003; 2004; Blakemore, 2003).

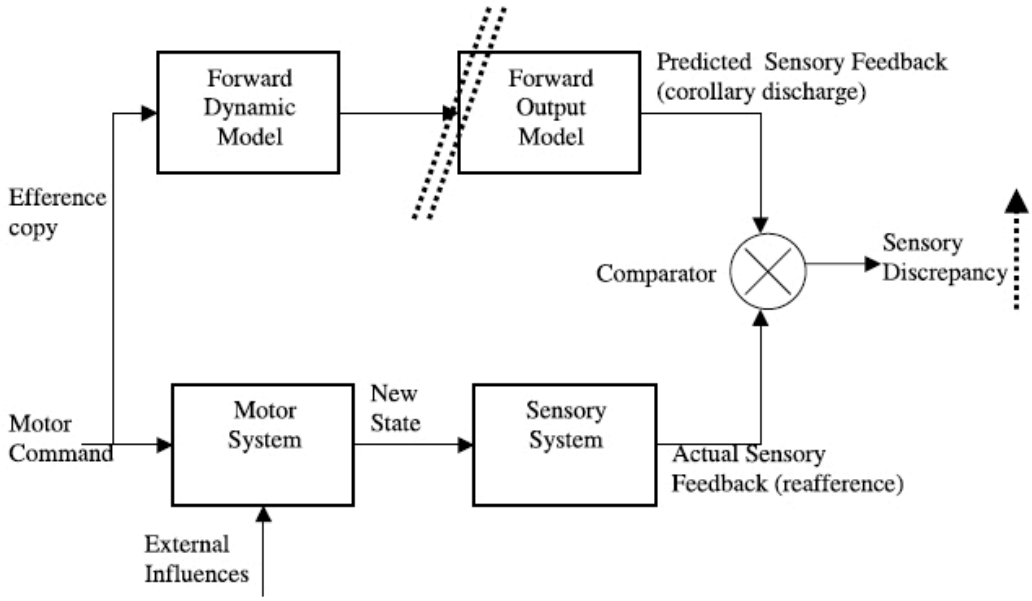


Fig. 5 The forward model makes a prediction of the sensory consequences of motor commands, which is compared with the real consequences of movement (reafference). Discrepancies resulting from this comparison can be used to update motor responses (Blakemore, 2003).

So far, performance monitoring in motor and non-motor tasks has mostly focused on self-generated errors. However, in everyday life also external factors such as technical malfunctions may interfere with goal achievement. In addition to monitoring deviations between the actual and intended goal, it is important for the agent to be able to locate the source of failure. If failure is due to an internal motor error, an update of the action may solve the problem. However, if failure is due a broken device, change of action will not be successful. Only if the cause of failure is known, appropriate actions can be undertaken to compensate failure. Therefore it is likely that the brain codes and responds differently to internal motor errors and external non-motor errors. As error perception has been consistently associated with pMFC activity and the update of motor plans in the cerebellum and the parietal cortex, the

question arises how these areas are affected by the presentation of motor (internal errors) and non-motor errors (external errors).

Research questions study 2:

Study 2 addresses three important aspects related to internal versus external sources of errors:

How does the magnitude of I) internal, II) external and III) total errors (the sum of internal and external error) influence brain activity?

To investigate the differential brain responses to internally and externally caused errors, a variant of the sensorimotor transformation task is used. Similar to study 1, subjects here have to handle a force-grip device. The cues are presented in form of a square along a horizontal line and the position of the dot determines the required motor response. After force grip manipulation subjects receive feedback about their performance in form of a second dot on the line. The spatial interval between these two dots describes the motor error. In 65% of the trials subjects are given correct feedback, in 35% subjects are given incorrect feedback about their motor performance, which always worsens their own performance (see Fig. 6).

It has been consistently shown that error monitoring in cognitive tasks activates the posterior medial prefrontal cortex (pMFC) and lateral prefrontal areas. On the other hand, studies that investigate the neural mechanisms of internal motor errors have focused on the parietal cortex and the cerebellum. The aim of study 2 is to determine in which brain areas the activity correlates with the size of the three above-mentioned error types.

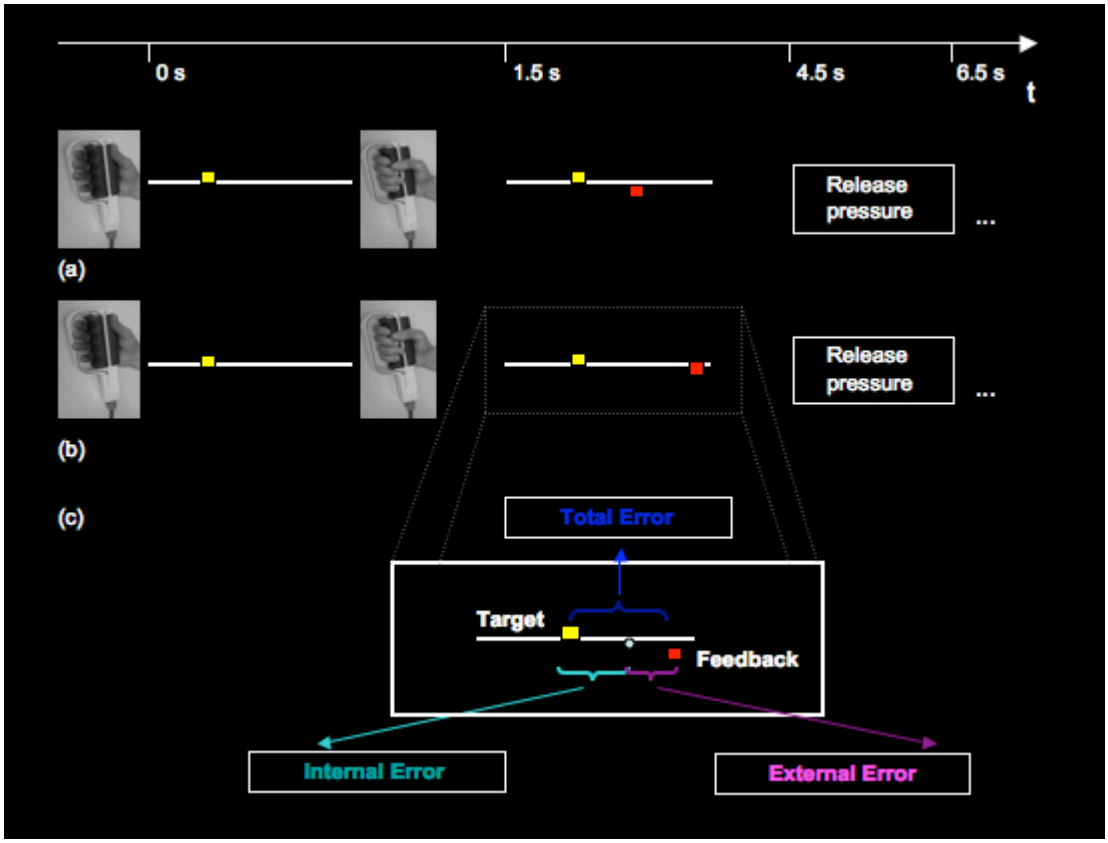


Fig. 6 A sensorimotor transformation with either internal error alone or internal plus additionally added external error (distortion) was used. a) In correct feedback trials the discrepancy between the yellow target square and the red feedback square is solely due to the subjects' performance error (internal error). No additional distortion is added. b) In incorrect feedback trials subjects are presented with a red square as feedback of their performance but unbeknown to them an additional error component is added to the feedback. This additional error component always increased the size of the error compared to the subjects' real motor error. c) The three measures were subjected to a parametric analysis. The gray circle is only inserted here (but not in the experiment) to indicate the feedback position if it were only affected by the subjects' performance. "Internal error" refers to the errors caused by the subject, "External error" refers to the externally added error and "Total error" describes the error fed back to subjects.

2.3 Sensorimotor transformation task and reward processing

Having addressed the role of spatial information and the source of feedback we next proceeded to investigate the role of reward in feedback processing.

Error and performance monitoring reliably trigger pMFC activity. This activity has been proposed to be triggered by the midbrain dopamine system (Schultz et al., 2000; Munte et al., 2007; Schultz et al., 2008). The aim of the third study was now to investigate brain activity linked to performance feedback at the level of the striatum, which is known to be involved in reward processing. In addition to feedback about performance, high performance was also rewarded with money in half of the trials.

Several areas have been implicated in the anticipation and processing of reward outcome, the most prominent structures being the orbitofrontal cortex and the striatum (Knutson et al., 2001; Knutson et al., 2001). Functionally, the striatum is divided into two substructures, the dorsal and the ventral striatum. The dorsal striatum is composed of the dorsal part of the caudate and the dorsal part of the putamen. On the other hand, the nucleus accumbens (NAcc), ventral part of the caudate and the ventral part of the putamen are counted to the ventral striatum (Fig. 7).

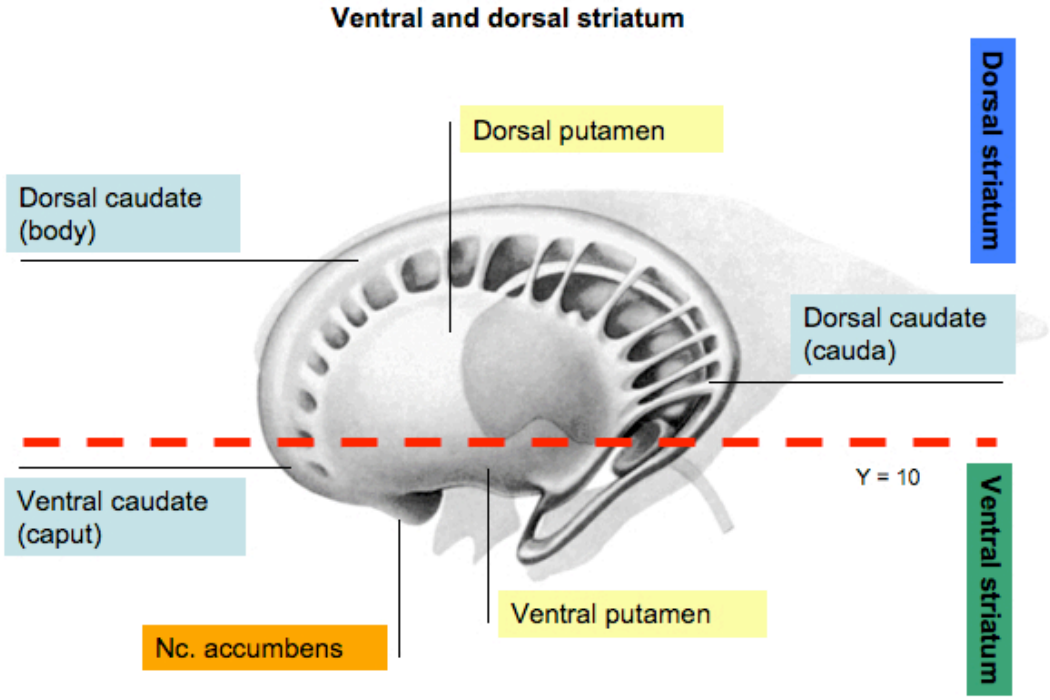


Fig. 7 The dorsal striatum (body and cauda of the caudate and the dorsal part of the putamen) and the ventral striatum (caudate's caput, ventral putamen and Nc. accumbens) are shown. The border between the dorsal and ventral striatum has been proposed to be at 10mm dorsal of the anterior commissure (Mawlawi et al., 2001).

There is evidence that the ventral striatum codes anticipation of reward while the dorsal striatum codes reward reception (Knutson & Coopers, 2005; Knutson & Gibbs, 2007; Knutson et al., 2001a; Knutson et al., 2001b, Coopers et al., 2009; Ballard & Knutson, 2009). However, functional imaging studies show an inconsistent pattern. Both in primates (Hollermann et al., 1998; Schultz et al., 2000) and in humans dorsal striatal activity has been linked to anticipation. Also activation of the ventral striatum has been found for anticipation of money (Breiter et al., 2001; Knutson et al., 2000,

Knutson et al., 2001, Roesch & Olson, 2007) as well as for reward outcome (Breiter et al., 2001; Delgado et al., 2000; Delgado et al., 2003; Delgado et al., 2004). Importantly, not only primary and secondary rewards but also written positive feedback about performance consistently activate the striatum (Shidara et al., 1998; Tricomi et al., 2004; Aron et al., 2004; Kirk et al., 2009; Sabatinelli et al., 2007).

The influence of reward on performance is still under debate. While in school and at workplaces incentives are used with the aim to enhance performance, psychologists have questioned if this is actually works (Deci et al., 1999; Frey, 2001). It has been suggested that subjects, to whom reward has been promised, feel pressured and therefore fail to perform well (Kohn, 1998). Deci and Ryan (1999) have put forward, that reward may impair subject's feeling of self-determination. This impaired self-determination may lead to a shift in motivation. This shift from intrinsic to extrinsic motivation may have detrimental effects on performance, especially on a long-term perspective.

In this study, we investigated two aspects of potential negative influence of monetary reward on task performance: First, we compared the subjects' performance levels in trials with and without monetary reward. And second, we analyzed the corresponding neural activity during these two trial types. Here, our focus was to ascertain whether trials with positive outcome feedback alone still elicit striatal activity, when presented among trials, which are also monetarily awarded. E.g. one may find it satisfying to perform well, but to know that in another situation this same performance would have been extrinsically rewarded may impair the value of the high performance alone.

Research questions study 3

Study 3 investigates how feedback processing is affected by the monetary gain that is linked to good performance. The central questions are:

I) How does performance level and II) how does monetary gain influence brain activity?

To assess these questions, a sensorimotor task similar to study 2 (Fig. 6) was used. However, two aspects were varied: I) only correct feedback is given, and II) on every trial a cue tells the subject whether monetary reward can be obtained or not. The reward was obtained in 50% of the trials if performed well. The monetary gain increased monotonically with performance level. In the other half of the trial no money could be obtained, regardless of subject's performance (Fig. 8). The main interest in this study lies on activation of the striatum during the different tasks and trial conditions.

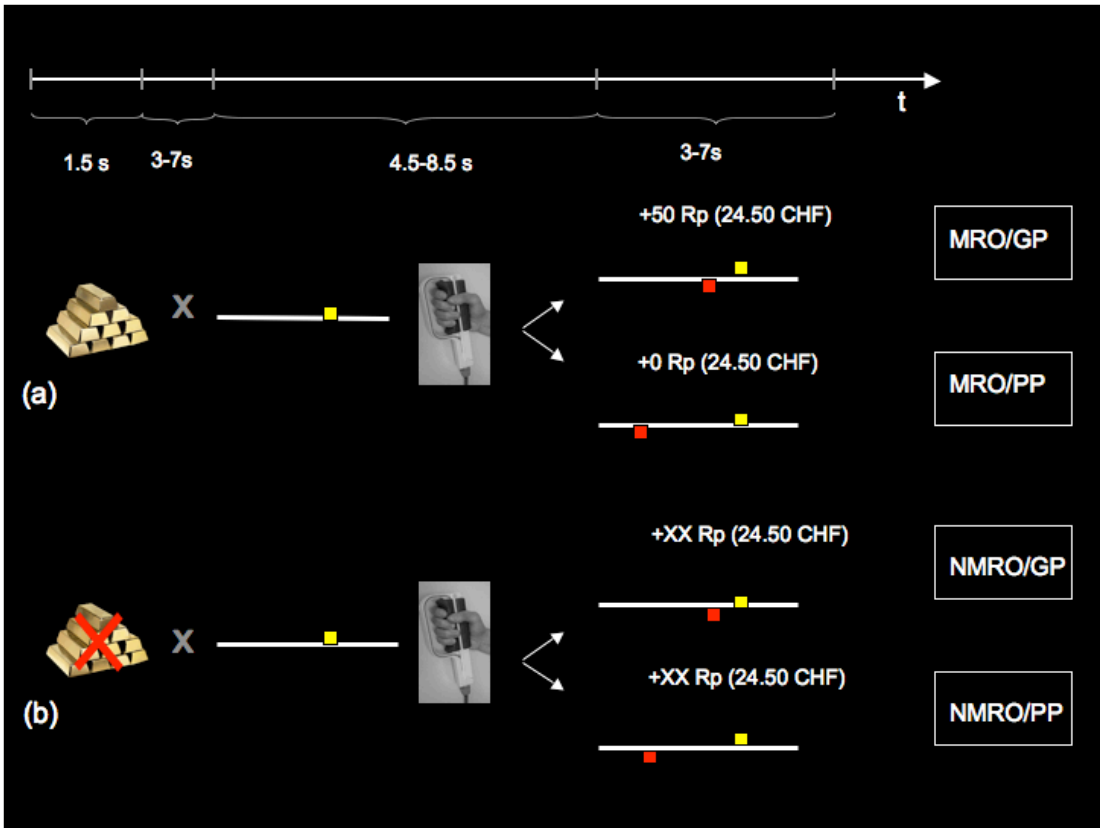


Fig. 8 There were two types of trials, monetary reward option trials (MRO) and no monetary reward option trials (NMRO). In the former, subjects earned money depending on their motor performance (a). In the latter, no money could be earned regardless of subject's performance (b). After the cue (gold bars or crossed gold bars), a yellow target square was presented above the line. Then, subjects had to manipulate the force-grip device and were given visual feedback about their performance in form of a red square appearing at the location below the line matching their applied force. Additionally, in PMR they were informed about the amount of money they just had earned and the cumulative total at that point. For the analysis the feedback was divided into two categories (good/poor). Good performance (GP) indicates outcomes that led to monetary gain, while poor performance (PP) indicates that it didn't.

3. Methods

In order to investigate the relation between cognitive processes and the activation of underlying brain areas, fMRI is the method of choice. Until 2008 over 19'000 peer-reviewed fMRI-studies had been published. Given that the first fMRI-study without exogenous agent was published in 1991, this corresponds to the publication of approximately three papers a day (Logothetis, 2008). Needless to say, that during the last twenty-five years this method has become very popular. Its popularity is mostly based on the advantages compared to other imaging methods like Electroencephalography (EEG) or Positron Emission Tomography (PET). First, no exogenous agents are necessary (non-invasive), and second, this method allows an unexcelled spatial resolution of about 2 to 3 mm and a temporal resolution of a few seconds. Due to the spatial resolution and in contrast to other imaging techniques, fMRI can be used to map deep sub-cortical structures.

3.1 The physical basics of MRI

The underlying physics of MRI can roughly be summarized in three steps.

First the subject is placed in a big magnet. Under normal conditions, nuclear magnetic dipoles in the body are randomly distributed, which results in zero magnetization. But once placed in a strong magnetic field, the subject's protons will align with the direction of the magnetic field and the subject becomes polarized.

Second, a radio wave impulse is applied (RF pulse). Protons have „spins", which have an orientation and a frequency. When the appropriate RF pulse frequency is chosen (Larmor frequency), the spins absorb energy and change orientation. Once the RF pulse is turned off, protons return to their original orientations and emit energy in form of radio waves.

Third, the emitted radio waves are measured. The T1 time constant describes how quickly the protons realign with the magnetic field (longitudinal magnetization, spin-lattice relaxation) and T2 time constant describes how quickly the protons emit energy when recovering to equilibrium (transverse magnetization, spin-spin relaxation). In T1 weighted images fat in tissue, has a high signal and is therefore represented by bright grey-scales, whereas cerebrospinal fluid (CSF), which contains

little fat, has a low signal and is therefore represented in dark. The opposite is the case in T2 weighted images, where CSF is bright and fat dark. Two factors contribute to the decay of transverse magnetization in T2, namely the molecular interactions and the local inhomogeneities of the magnetic field. The combined time constant is called T2*. E.g. Echo Planar Imaging (EPI) technique is sensitive to changes in T2* and from it's measurements a spatial image can be constructed (Weishaupt et al., 2009).

3.2 The physiological basics of fMRI

The last chapter sketched the physical basis of anatomical images. But the main interest of cognitive neuroscientists lies not so much in the anatomical structures of the brain, but in its functional behavior (i.e. its "activity"). T2* weighted images can be used to obtain functional measurements of brain activity. The key mechanism for functional images is the Blood Oxygenation Level Dependent (BOLD) contrast. The BOLD contrast measures inhomogeneities in the magnetic field due to changes in the level of oxygene in the blood. Oxygenated hemoglobine has diamagnetic characteristics, which do not influence the magnetic field, whereas deoxygenated hemoglobine has parametric characteristics (i.e. it is magnetic), which affects the local magnetic field homogeneity and leads to a loss of signal. The exact causal link leading from neuronal activity to changes in oxygen concentration in the blood and changes in regional cerebral blood flow (rCBF) is not totally understood yet. The current view is that an over-compensatory increase of rCBF following neural activity leads to a relative diminuation of deoxygenated hemoglobine in the blood, and this in turn causes higher T2* signal intensity (Logothetis 2002). The BOLD signal displays a characteristic temporal profile. After the presentation of a stimulus, in some cases an initial decrease in the fMRI signal, known as the "initial dip", can be observed (Buxton et al., 2004). The BOLD-signal then rises and peaks 4-6 seconds after stimulus and returns to baseline after approximately up to 30 seconds. These characteristics can vary between regions and subjects. But one may ask what exactly is reflected by the BOLD signal? It is frequently assumed that the BOLD signal is an *indirect* indicator of neural activity. In early experiments comparing human BOLD signals and monkey electrophysiological data from similar paradigms, BOLD signals were found to be correlated with action potentials (Buxton et al., 2004; Rees et al., 2000). Logothetis and colleagues (2001) combined BOLD fMRI and electrophysiological recordings and found that BOLD activity is more closely related

to local field potentials, which reflect summation of post-synaptic potentials. The current conclusion is that the BOLD signal seems to be more strongly correlated to postsynaptic activity and seems to reflect the input to a neuronal population as well as its intrinsic processing (Laurizen, 2005). However, more recent research suggests that the BOLD signal can be influenced by other factors than neuronal activity only (Schummers et al., 2008; Sirotin & Das 2009).

3.3 Preprocessing of data: realignment, normalization & smoothing

Before the functional T2* weighted images are subjected to statistical analysis, they have to be preprocessed. These preprocessing stages are outlined in the following paragraphs.

3.3.1 Realignment

First the T2* weighted images have to be realigned. Even small head movements can be a major problem in imaging as they can substantially decrease the statistical power. Further, movements may be correlated with the task and can systematically distort the quality of the data and lead to false positives. The aim of realigning the data is therefore to eliminate head movement artefacts.

The criterion chosen for realignment is the minimization of the squared signal differences between source and reference image. The realignment procedure assumes that all movements are those of a rigid body (i.e. that the shape of the brain remains constant during the measurement).

The realignment procedure includes two steps: The first step is called registration, the goal of which is to define six parameters that describe a rigid body transformation between the source and a reference image. Commonly the T2* weighted images are realigned to the first slice, though other options are possible. The second step contains the actual transformation of the images, where they are re-sampled according to the transformation determined previously. The realignment parameters can be taken into account when modeling the data (Jancke et al., 2005).

3.3.2 Spatial normalization

In a second step, the images are spatially normalized. Brains vary considerably in shape and size (Jancke et al., 2005), which is a problem when averaging data across

multiple subjects to increase statistical power. If images with different shapes and sizes are simply overlaid on top of each other, the statistical power would be considerably reduced. To allow for averaging of multi-subject data and extrapolating findings to the population as a whole, the brains are normalized. The objective of the spatial normalization is to “warp” the images such that anatomically corresponding regions from different subjects are as close together as possible. This approach is very powerful, but it has limitation in that there is not necessarily always a perfect match between structure and function. So the spatial normalization based on anatomy is limited to correct large-scale differences.

3.3.3 Spatial smoothing

Third, the functional T2* weighted images are spatially smoothed. The BOLD response even to a single neural event has a certain spatial expansion in the vasculature. Due to this extended response the activation level measured in neighbouring voxels is not independent of each other (Jancke et al., 2005). To consider this interdependence in the statistical analysis the data is artificially smoothed. The smoothing procedure induces a predefined statistical dependency between neigbouring voxels and eliminates high frequency spatial noise. The spatial smoothing acts as a low pass filter and consequently increases signal to noise ratio (SNR) for activations that are extended over several voxels. Smoothing is done by convolving the T2* weighted images with a 3D Gaussian which is defined by its full width at half maximum (FWHM). Each voxel after smoothing effectively becomes the result of applying a weighted region of interest.

3.4 Analysis of fMRI data: General Linear Model (GLM)

Once the data is preprocessed, the main statistical analysis can be performed. To analyze the data, a statistical approach called the General Linear Model (GLM) was developed by Friston and colleagues (1995). This model allows to make inferences about the effects of interest by postulating relationships between the experimental manipulations and the observed data. The GLM follows a “mass-univariate” single voxel regression approach which can be described as $Y = X1\beta1 + e$. Hereby, Y represents the measured data and can be approximated with a linear combinations of time series in X. The design matrix X embodies all available knowledge about experimentally controlled factors and potential confounds, while e describes the

error, the additive noise and has a normal distribution. The parameter β can be estimated using ordinary least square (OLS) and describes the weight of X.

Several aspects need to be taken into account when establishing a GLM model for fMRI data. First, the BOLD responses have a temporally delayed and dispersed form. Second, the BOLD signal includes substantial amounts of low-frequency noise and third the data are serially correlated, which violates the assumptions of the noise model in the standard GLM. The solution to the first problem is to convolve the input time series with the brain's standard hemodynamic response function (HRF). To solve the problem of low-frequency noise, a high pass filter can be applied to the data, which suppresses low frequency signal components. To address the problem of autocorrelation mainly two options have been proposed. The first one suggests the so-called pre-coloring of the data, namely to impose some known autocorrelation structure on the data, the second option proposes the pre-whitening of the data by using an enhanced noise model with multiple error covariance components and to use the estimated autocorrelation to specify the filter matrix for whitening the data (Kiebel et al., 2003).

3.5 Experimental designs

The structure of the design matrix X is directly influenced by the experimental design. There are several types of experimental designs, the two most frequently used ones are block and event-related designs.

In a *block design*, two or more conditions are alternated in temporally extended blocks that typically contain several trials each. Each block will have a duration of a certain number of fMRI scans and within each block only one condition is presented. Using a block design has one main advantage. The increase in fMRI signal in response to a stimulus is additive. This means that the amplitude of the hemodynamic response function (HRF) increases when multiple stimuli are presented in rapid succession. When each block is alternated with a rest condition in which the HRF has enough time to return to baseline, a maximum amount of variability is introduced in the signal. Therefore, block designs offer considerable statistical power. But block designs have two important drawbacks: Since the stimulus types cannot be presented in a random sequence, the stimulus type of the next trial is predictable. As a consequence, participants can become aware of the order of the events, which may induce expectations, which in return influence the

BOLD-signal. The second drawback concerns the classification of trials. In some designs (as e.g. in the third experiment), the classification of trials only becomes possible *after the experiment*, when subjects have given their answer (e.g. high vs. low performance). In these cases it is not possible to analyze the data by pre-sorted blocks.

The second type of experimental design is the so-called *event related design*, in which the stimulus types are presented in a randomized order and the timecourse of the HRF following each stimulus presentation can be estimated. The multiple HRF's following a single type of stimulus can be averaged. The event-related design however has important advantages. For example, it permits the abovementioned post-hoc classification of trials (e.g. according to performance of subjects). This allows for more real world testing, however, the statistical power of event related designs is inherently low, because the signal change in the BOLD fMRI signal following a single stimulus presentation is small (Aguirre et al., 2002). To improve statistical power in event-related designs, variable inter-stimulus interval (ISI) timing can be introduced. Price and colleagues (1999) demonstrated the superior sensibility of event-related designs compared to epoch-related designs using ISI.

3.6 Contrast Construction

To test for specific effects, statistical contrasts between different experimental conditions are used. These contrasts allow to focus on specific features of the experiment. The logic of contrasts is subtractive. Two or more conditions can be contrasted. E.g. a condition like reading can be contrasted to baseline activity. In that case the baseline brain activity will be subtracted from that obtained during reading and the resulting difference will be tested for significance. The resulting contrast will then display the neuronal network involved in reading. It is also possible to contrast to stimulus types, e.g. reading words vs. reading non words. Here the „reading" component remains the same and any differential activation will indicate a difference in the neural processing between words and non-words. Contrast specification and the interpretation of results totally depend on model specification which in turn are dictated by the experiment design (Price et al., 1999).

3.7 Group-level interference

The analyses outlined above only deal with single subjects. To make interferences on group level, further statistical tests need to be performed. There are several approaches that allow group level interferences. The *fixed effects* approach assumes that parameters are fixed properties of the sample and that all variability is restricted to intra-subject variability (e.g. measurement errors) and the probability distribution of the data has the same form for each individual and the same parameters. This approach ensures lots of power (proportional to number of scans) but results are only valid for the group studied and can't be generalized to the population. In contrast, the *random effects* approach assumes that model parameters are probabilistically distributed in the population and that variance is due to inter-subject variability. Further it is assumed that the probability distribution of the data has the same form for each individual but the parameters vary across individuals. The random effect approach is much less powerful (proportional to number of subjects), but results can in principle be generalized to the population.

3.8 Statistics and statistical thresholds

Once the data has been modeled, the errors have been estimated, and the contrasts have been set up, the next step is to use a statistical test (typically a T- or an F-test) to determine for each voxel separately whether a specific linear combination of estimated parameters is significantly different from zero. In other words, does any linear combination of the predictor variables defined in the design matrix explain a significant amount of variance in the BOLD fMRI dataset at that voxel. The explained variance given by a linear combination of parameters in the parameter matrix is statistically compared to the unexplained variance in the error matrix. The result is a T-score (or F-score) for each voxel and for each linear combination of predictor variables reflecting how well the observed BOLD fMRI timecourse is explained (Kiebel et al., 2003).

To avoid false positives, a probability threshold is set in the statistical test. However, it is important to realize that this statistical test is performed for each voxel separately. If ten thousand voxels are tested at a probability threshold of 5%, five hundred voxels will show spurious significant activation by chance (i.e. a statistical type I error). These 'fake' activations are known as false positives. The desired

solution is to choose a statistical threshold that keeps the family-wise error below 5%. In some cases, however, this family-wise error correction procedure on voxel level is too restrictive and the data can be tested on cluster level. If one has a good hypothesis about where an activation should be, the search volume can be reduced to this region of interest (ROI). The first and second studies in this thesis report significant cluster level activation, the analysis of the third study is based on an ROI-analysis .

3.9 Design and the present fMRI studies

The T2* weighted images were preprocessed as suggested by Friston and colleagues (2003). Specifically, they were first realigned to reduce motion artifacts, then spatially normalized to enable inter-subject data averaging and finally smoothed to account for the fact of the intercorrelation of the neighbouring voxels. The experiments consisted of event-related designs and as suggested by Price and colleagues (1999) we used variable ISI presentation to improve detection rate in event-related experiments.

Since we were also interested in the influence of varying behavioral responses on brain activity, we parametrically modulated them. It is possible to modulate defined events in the design matrix X by some parametric variables (Büchel et al., 1996; Büchel et al., 1998). Based on the assumption that BOLD signal varies with the amount of neuronal activity, parametric modulation of events can reveal information about the relationship between e.g. a behavioral response and the BOLD signal. Parametric analyses were performed on the one hand to control certain effects (like unequal force requirements between conditions) and on the other hand to e.g. investigate a graded impact of a behavioral component (motor and external error). The data was analyzed with the GLM as formulated by Friston and colleagues (1995). We used a random effects analysis which enables us to generalize our results and reported significant data on corrected cluster level ($p < 0.05$). For exact modeling and analysis information for the three experiments reported in this thesis, see the respective method section.

4. Study 1

Spatial characteristics of motor responses and visual cues differentially influence posterior parietal activity

Karin Nadig, Lutz Jäncke, Roger Lüchinger and Kai Lutz

4.1 Abstract

The inferior posterior parietal cortex (infPPC) and the intraparietal sulcus (IPS) are widely known to be involved in the planning of movements as well as in the analysis of spatial information in visual stimuli. To systematically investigate the influence of the spatial properties of motor responses and visual information in humans on infPPC and IPS activation, we employed a sensorimotor task performed during fMRI measurement. The spatial characteristics of motor responses and visual stimuli were varied, yielding four different task combinations. InfPPC and IPS activation was lowest for isometric motor responses that are linked to a visual stimulus containing no spatial information, while somewhat greater activity was observed for spatially encoded sensory information linked to an isometric movement. Greater increase in activity was associated with the two conditions involving dynamic movement. Dynamic motor responses activate a large parieto-frontal network compared to the isometric motor response. On the other hand, the visual stimuli analysis in the spatial judgement condition compared with the visual stimuli requiring no spatial judgment activates only little of the supramarginal gyrus. Consequently, infPPC and IPS activation differences are strongly influenced by the spatial requirements of the movements and to a much lesser extent by the spatial characteristics of visual stimuli.

4.2 Introduction

Successful integration of visual information into motor actions is essential for the smooth course of movement in everyday life. The transformation of sensory input and its contribution to motor behavior has been investigated extensively over the past two decades (for review see Culham et al., 2006). In this context, three types of sensorimotor tasks have mainly been used to elucidate the sensorimotor network: (1) pointing, reaching and grasping tasks (e.g. Binkofski et al., 1999; Frey et al., 2005; Culham & Valyear 2006; Grol et al., 2007), (2) arbitrary associative tasks requiring

each stimulus to be linked to a specific, discrete movement (e.g. Toni et al., 2001a; Toni et al., 2001b; Thoenissen et al., 2002; Cavina-Pratesi et al., 2006; Majdandzic et al., 2007; Mars et al., 2007), and (3) sensorimotor transformation tasks, which involve target-directed tool manipulation (e.g. Floyer-Lea & Matthews, 2004; Floyer-Lea & Matthews, 2005; Imamizu et al., 2007; Stark & Zohary, 2008). Common to all the above-mentioned studies is activity in the inferior posterior parietal cortex (infPPC) and in the intraparietal sulcus (IPS), which serves as sensorimotor integration site (Grefkes & Fink, 2005)

Classical sensorimotor tasks consist of two parts – the processing of a sensory instructive cue and the generation of a motor response. Both of these parts can, for example, vary in spatial characteristics, and either do or do not contain spatial information. Spatial instructive cues can take the form of pictures, in which an element's position provides information about the required manipulation. Non-spatial instructive cues might be presented as colors that can also give information about a required manipulation. The motor response can also vary in its spatial characteristics, by requiring movement coordination in space (dynamic movement) or none (isometric movement).

Despite extensive research carried out in the past few years, the contribution of the spatial characteristics of motor responses and sensory information has hardly been investigated at all. This is astonishing since it is known that IPS and infPPC are essential for analyzing spatial properties of visual stimuli as well as for movement planning. The aim of this study was to further explore the role of the IPS and infPPC in processing spatial information and to extend the findings into the domain of visuomotor integration. To address this question systematically, we used a fully balanced 2x2 factorial design in which the spatial properties of sensory information and motor response were varied, thus resulting in four different task conditions.

We used fMRI to measure human brain activity during the performance of the four task conditions, each of which required the association of visual stimuli with motor responses. Based on pertinent previous research, we expected to find IPS and infPPC activity in all four conditions, but with a changing degree of spatial motor and visual stimulus characteristics. Explicitly, we expected more IPS and infPPC activity for the dynamic motor task than for the isometric motor task, because dynamic movements require more agonist/antagonist interaction than isometric movements and therefore rely on more muscle coordination. Further, since the infPPC is part of the visual dorsal stream, which is traditionally thought to be responsible for extracting

information about spatial characteristics (Ungerleider & Mishkin, 1982), we predicted more infPPC activity for the visual stimulus condition containing spatial information. Consequently, we expected a gradual increase of IPS and infPPC involvement from only a low level of activity in the isometric motor condition linked to a non-spatial visual stimulus, to more in the isometric motor condition liked to a spatial visual stimulus.

4.3 Methods

4.3.1 Participants

The participants were sixteen healthy right-handed (Oldfield, 1971) subjects (mean age: 24.8 years, SD: 2.0). All of them had normal or corrected-to-normal vision and none had a history of neurological, major medical, or psychiatric disorder. One participant was excluded because he switched hands during the experiment to manipulate the instrument. The remaining 15 participants were 11 females and 4 males. All subjects gave written informed consent. The participants were naïve as to the purpose of the experiment and received 40 CHF for participation (approximately 40 US Dollars). The study was approved by the local ethics committee; tasks and testing procedures were in accordance with the institutional guidelines and the study conforms to the Helsinki Declaration.

4.3.2 Apparatus, stimuli and procedure

Two different instruments were used in this experiment, a force-grip device and a lever-adjustment device. The lever-adjustment device was used as a modified version of the visual analog scale (COVAS, Medoc (R), Haifa, Israel), which was connected via a self-made USB interface to the Presentation 11.2 experimental software (Neurobehavioral Systems, Inc, Albany, USA). The lever-adjustment device consisted of a box with a horizontal slit on its surface. To operate this instrument, subjects had to grasp the lever and move it along the horizontal dimension. This instrument required a spatial manipulation of the lever, involving several agonist and antagonist muscle pairs. The second instrument was an MRI-compatible isometric force-grip measurement system (isometric dynamometer, Sensory-Motor Systems Laboratory, ETH Zurich and University of Zurich), which measured force from 0 to 100 N in 8 bit resolution. This instrument enabled us to provoke isometric motor responses, which comprised only the application of force but no spatial displacement.

This isometric motor response does not rely on the use of agonist and antagonist muscles.

Two types of sensory cues were linked to the two types of instruments. One sensory cue type consisted of a horizontal line with a square above it. The total length of the line was 256 pixels, 12 cm long and comprised a visual angle of approximately 7 degrees. Two small squares (5x5 mm), one above and one below the line served as target / feedback cues. The spatial position of the target cue on the horizontal line contained information about the required manipulation. The second square, which was provided for feedback about the manipulation, was placed below the line. A spatial judgment between these two squares had to be performed to determine the motor error. The other sensory cue type consisted of a colored quadrant. As target cue, one quadrant (5x5 cm; visual angle of approximately 3 degrees) was presented in the upper right part of the screen. The quadrant's color contained information about the required manipulation. After manipulation, feedback was given in the form of a second colored quadrant below the target quadrant. In this case, the error was assessed as the difference in color between these two quadrants, and no spatial judgment was required. The color scale used in the "color"- condition ranged from white (R = 255; G = 255; B = 255) through orange (R = 255; G = 0; B = 255) to red (R = 255; G = 0; B = 0). In this way, the target as well as the feedback cues could be quasi-continuously scaled by varying the green and blue component of the RGB spectrum. The transformation of the applied instrument manipulation to visual feedback was linear for both instrument types; that is, the further the lever was moved to the right, or the harder the force-grip device was pressed, the further the second dot appeared to the right hand side of the line and the redder the quadrant's color was. For example, minimum manipulation (lever-adjustment device less than 5 mm, force-grip device less than 10 N) was coded by white, whereas maximum manipulation (lever-adjustment device 10 cm to the right, force-grip ≥ 100 N) was translated into a red color. The position of the target and the color of the quadrant were generated pseudo-randomly for each participant.

4.3.3 Experimental setup

During the scanning session, participants lay supine in the scanner. Head movements were minimized by an adjustable vacuum cushion. Visual stimuli were projected onto a mirror above the participants' heads. Motor responses were recorded via magnetic resonance-compatible lever-adjustment and a force-grip

instrument. The lever-adjustment instrument was positioned over the middle part of the participant's abdomen, whereas the force-grip instrument was placed in their right hand. Stimulus presentation and response collection were controlled by "Presentation 11.2" software (Neurobehavioral Systems, Inc, Albany, USA).

4.3.4 Behavioral procedure

In order to investigate the influence of spatial components of the visual input and motor output on the infPPC systematically, a visuomotor transformation task was used in a 2x2 factorial fMRI paradigm. Within this task, both the instrument manipulation and paired visual information were varied systematically in their spatial property. Two kinds of instruments were used in the motor part of the task, one requiring limb coordination in space and the other not. In addition, two kinds of target and feedback cues were also presented, one containing spatial information and the other not.

The combinations of the different motor and visual conditions were altered in a systematic fashion, resulting in four tasks that varied in their spatial components of visual information and their instrument manipulation requirement. Each condition contained 70 trials, each lasting approximately 7.5 seconds. The target cue was presented for 3 seconds and subjects had 2.5 seconds to answer. Feedback presentation lasted for 3 seconds and the request to release the handle or to reset the lever was presented for 1.5 seconds. Ten null events lasting 10 seconds each were included in a pseudo-randomized order to allow a resting activity (baseline) to be calculated. The whole experiment comprised 280 trials (4 x 70), with a total duration of about 60 min.

The "force-grip/color" condition consisted of an isometric movement and a visual cue containing no spatial information (Fig. 1a). First, a colored quadrant was presented to the subjects. As instructed, the subjects then pressed the force-grip device and received visual feedback in the form of a second quadrant of different color (reflecting the force application transformed into color). This was positioned below the first quadrant. The relative color difference between the two reflected the accuracy of force applied by the subject. After the feedback had been presented for three seconds, the subjects were requested to release the pressure on the force-grip device, and a new trial was started.

The "force-grip/dot-on-a-line" condition consisted of an instructive cue containing spatial information and an isometric manipulation (Fig. 1b) containing no spatial

components. In this condition, a line with a dot above it was presented to the subjects. They then applied force to the force-grip device, and feedback was given about the manipulation in the form of a second dot presented below the line. The spatial distance between the two dots represented the motor response error. Again, subjects were asked to release force on the force-grip device, and a new trial began.

In the “lever-adjustment/color” condition, the manipulation was a dynamic one, containing spatial elements, whereas the instructive cue did not comprise spatial elements (Fig. 1c). As in the “force-grip/color” condition, a colored quadrant was presented to subjects. However, instead of manipulating a force-grip device, they now had to move the lever on the lever-adjustment device. Again, subjects were presented with a second colored quadrant reflecting the outcome of their manipulation, and were then asked to reset the lever by shifting it to the left-most side of the slit.

Finally, the “lever-adjustment/dot-on-a-line” condition included a dynamic motor response and spatial information on the sensory side (Fig. 1d). Subjects were presented with a dot above the line. They then moved the lever on the lever-adjustment device and were given feedback. Again, they were asked to reset the lever to the left-most position of the lever-adjustment device, and a new trial was subsequently presented.

Between the runs, the instruments were exchanged and placed in the subjects’ right hands.

At the end of the experiment, subjects completed a self constructed questionnaire to provide information about the difficulty experienced in each task.

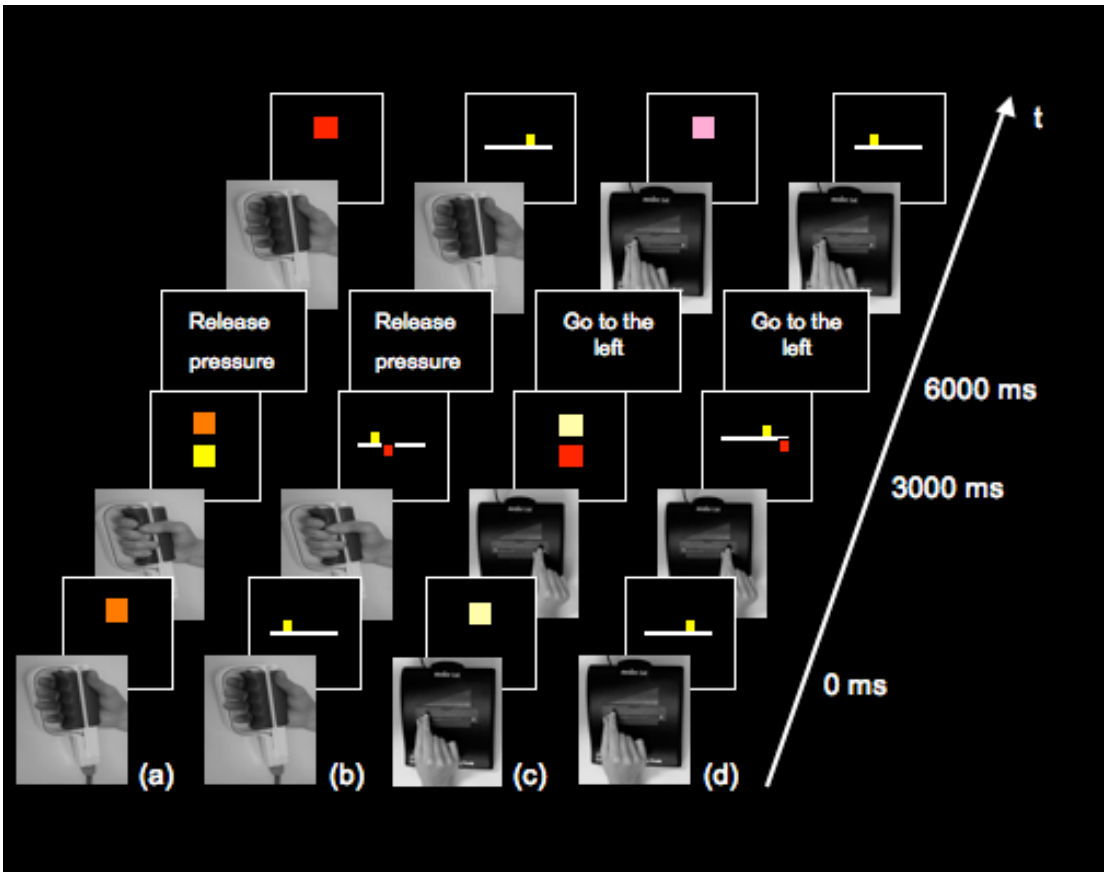


Fig. 1 Experimental task. At time point 0, subjects were presented with a target (either a colored square or a dot above a horizontal line), upon which they had to manipulate the tool in their hand. After three seconds, they were given feedback about their performance, lasting for a further three seconds. At the end, subjects were instructed to release the pressure on the force-grip device or to reset the lever at the leftmost position. The four conditions are depicted here, from left to right: the "force-grip/color" condition, which contained no spatial properties either on the feedback or on the motor side (a) the "force-grip/color" condition which contained no spatial elements (b) the "force-grip/dot-on-a-line" condition which contained spatial elements on the sensory side, but none on the motor side) (c) the "lever-adjustment/color" condition, which required spatial coordination on the motor side, but none on the feedback side (d) the "lever-adjustment/ dot-on-a-line" condition which contained spatial properties on both sides

4.3.5 Behavioral analysis

In order to test the comparability of the four task conditions in terms of the participants' performance, the reaction times and the error size associated with each condition were subjected to statistical analysis. Reaction time was defined as the delay between stimulus presentation and start of the movement, and error size was computed as the difference between the cue and feedback stimulus pixel positions. A Kolomogorv-Smirnov test (K-S test) was conducted to test whether the data deviated

from normal distribution. Where data conformed to the requirements of an ANOVA, 2x2 between-subject ANOVAs were conducted through the dependent variables of reaction time and "size of error", using the factors "instrument" (2 levels: force-grip device and lever-adjustment device) and "visual information" (2 levels: “color” and “dot-on-a-line”).

To check that the reaction time does not depend on spatial characteristics of the visual stimuli, an additional behavioral experiment was conducted and evaluated with a dependent two-tailed T-test. Here, subjects were asked to manipulate either the force-grip device or the lever-adjustment device as quickly as possible upon a go signal. The go-signal consisted to the letters “GO” and therefore contained neither specific spatial nor color information. Subjects were not given any feedback about their performance.

At the end of the experiment, subjects were asked to complete a questionnaire in which they had to report upon which task they considered the most difficult and which the easiest. This data was analyzed with a Chi-square test.

To exclude the possibility that colors are mentally represented on a spatially ordered scale, e.g. light colors on the left and darker colors on the right, we applied a modified version of the SNARC-paradigm (Dehaene et al., 1993) accordingly. Subjects were presented with bars, in either a horizontal or vertical orientation, and had to press a button with the right hand when the bar was vertically oriented or with the left when the bars were horizontally orientated. The color range extended across nine discrete levels from white through orange to red. For calculation of the reaction time, the average reaction time of the first four (in RGB: 255, 255, 253 (white); 255, 255,189 (light yellow); 255, 255,126 (yellow); 255, 255, 63 (dark yellow)) and the average reaction time of the last four colors (in rgb: 255, 189, 0 (orange); 255, 126,0 (reddish orange); 255, 63, 0 (red); 255, 0, 0 (dark red)) were taken into account. The reaction time was analyzed by a 2x2 ANOVA (2 levels: color (white to yellow; orange to red), 2 levels: bar orientation).

If not mentioned otherwise, all data have been corrected for multiple comparisons (Bonferroni correction) to minimize Type I error and alpha-level was set to 0.05. All behavioral data was analyzed with SPSS Version 14.0, Chicago, Illinois, USA, http://www.spss.com.

4.3.6 Imaging

Functional magnetic resonance imaging was performed on a Philips Achieva 3-T whole-body MRI system (Philips Medical Systems, Best, The Netherlands) at the University Hospital of Zurich. Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted three-dimensional spoiled gradient echo pulse sequence (180 slices, TR = 20 ms, TE = 2.3 ms, flip angle = 20°, FOV = 220 mm × 220 mm x 135 mm, matrix size = 224 x 187, voxel size = 0.98 mm × 1.18 mm × 0.75 mm, resliced to 0.86 mm x 0.86 mm x 0.75 mm).

Functional data for the behavioral tasks was obtained from 240 scans per run, 33 transverse slices covering the whole brain using a Sensitivity Encoded (SENSE, factor 2.0) single-shot echo planar imaging (EPI) technique (repetition time, TR = 2.5 s; echo time, TE = 35 ms; field of view = 220 mm × 220 mm x 132 mm; flip angle = 78°; matrix size = 80 × 80; voxel size = 2.75 mm × 2.75 mm × 4 mm, resliced to 1.72 mm x 1.72 mm x 4 mm). The beginning of stimulus presentation was synchronized with the beginning of the 4th dynamic EPI scan by a TTL signal, discarding the first three EPI scans.

4.3.7 Image analysis and statistical inference

Image analysis was performed on a PC using MATLAB 7.4.0 (R2007a) (Mathworks Inc., Natiek, MA, USA) and SPM5 (http://fil.ion.ucl.ac.uk/spm). All images were realigned to the first volume, corrected for slice acquisition time, normalized (2 mm × 2 mm × 2 mm) into standard stereotactical space (EPI-template provided by the Montreal Neurological Institute, MNI brain), and smoothed using a 6mm full-width-at-half-maximum (FWHM) Gaussian kernel. Activated voxels were identified by the “General Linear Model” approach. At the first level of analysis a statistical model was computed for each subject. For the first level of analysis, one session was defined for each type of condition (Level-adjustment/dot-on-a-line; Level-adjustment/color; Force-grip/dot-on-a-line; Force-grip/color). Each session consisted of three regressors (onset target presentation, duration 6 sec; onset reset lever/release force-grip device, duration 1.5 sec; onset missed trials, duration 7.5 sec). Due to a high inter-correlation of the signal between the different events (cue presentation, movement and feedback presentation), only one event lasting 6 seconds was modeled. A box-car model was applied, which was convolved with the canonical hemodynamic response, thus eliminating high-frequency noise. A statistical parametric map of the *T*-statistic [SPM(*T*)] was generated for each voxel to test hypotheses about regionally-specific condition effects. Linear contrasts against null events (10 seconds rest epochs, blank screen and with fixation cross) were

employed for each subject and condition, as suggested by Friston and colleagues (Friston et al., 1995). A random effect "second-level-analysis" was employed to test activation for population effects and compare the difference between the conditions. The "con-images" obtained from the individual subjects were therefore further smoothed by an 8 mm FWHM Gaussian kernel to ameliorate differences in intersubject localization and subjected to voxelwise one sample t-tests. In total, the data has been smoothed by 10 mm FWHM (6^2 + 8^2)^(1/2). Statistical inference is based on cluster level corrected for multiple comparisons. Clusters were reported when $p < 0.05$ and number of voxels > 25.

A conjunction analysis was performed to test the hypothesis that all four task conditions activate the infPPC and IPS. In conjunction analysis, the individual contrasts, thresholded at $p > 0.001$ are adjoint with a logical "and" function. The probability of a voxel satisfying this criterion by chance is $p > 0.001^4$, which is a very conservative criterion.

Areas revealed by the conjunction were subjected to a ROI analysis (MarsBar) to calculate percent signal change. Percent signal change values were analyzed with a repeated measure within-subject ANOVA and eta^2 as well as percentage of explained variance ($v^2 = (eta^2/(1\text{-}eta^2)^{1/2})$ were determined. This procedure allows to differentiate how much of the experimentally induced signal variance is explained by the motor instrument and by visual stimuli, respectively, in the regions commonly activated by all conditions jointly.

4.4 Results

4.4.1 Behavioral result

To test the comparability of the four task conditions with respect to subjects' performance, we analyzed reaction time and error size by means of repeated measures ANOVA. Behavioral data obtained during the scanning session is summarized in Fig. 2 and 3. The prerequisite Kolmogorov-Smirnov test showed that the reaction time distribution did not deviate from a normal distribution for the two instruments (force-grip device: $P = 0.958$; lever-adjustment device: $P = 0.726$) or for the sensory stimuli (color: $p = 0.984$; dot-on-a-line: $P = 0.997$). Similarly, error size was normally distributed among the four conditions ("force-grip/color" condition: $P = 0.062$; "lever-adjustment/color" condition: $P = 0.279$; "force-grip/dot-on-a-line" condition: $P = 0.983$; "lever-adjustment/dot-on-a-line"-condition: $P = 0.896$).

Analysis of error size by 2x2 repeated measures ANOVA showed that subjects performed significantly better with the lever-adjustment device than with the force-grip device ($F_{1,14}$= 5.2, P = 0.038) (Fig. 2). In addition, the error size associated with the “dot-on-a-line” condition was significantly lower than during the “color”- condition ($F_{1,14}$= 4.9, P = 0.043) (Fig. 2), but no significant link was found between instrument manipulation and transformation ($F_{1,14}$= 0.008, P = 0.931).

A 2x2 repeated measures ANOVA for reaction time revealed a significant main effect between the different instruments used during the experiment: the time from imperative stimulus presentation to onset of subjects’ motor action was significantly shorter for the force-grip device (reaction time force-grip device) than for manipulation with the lever-adjustment device (reaction time lever-adjustment device) ($F_{1,14}$= 39.6, P < 0.001) (Fig. 3). There was no main effect for the sensory conditions ($F_{1,14}$ = 1.082, P = 0.316) (Fig. 3) and no significant interaction effect ($F_{1,14}$ = 1.479, P = 0.244).

A control experiment was conducted and results were analyzed with a dependent two-tailed t-test to ensure that the reaction time depends only on the motor demands and not on the visual information. The results show a significant difference in reaction time associated with use of the two instruments, independent of the visual transformation (Main Effect "instrument": T = 5.871, df = 9, P <0.001).

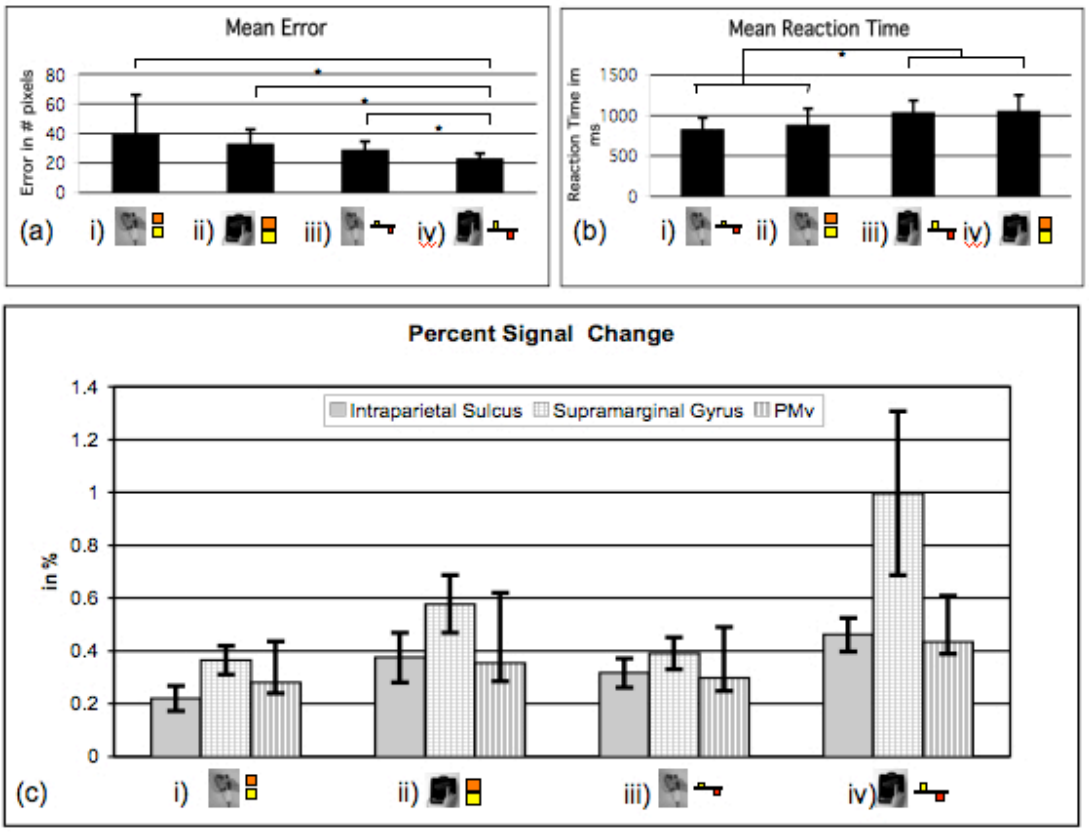
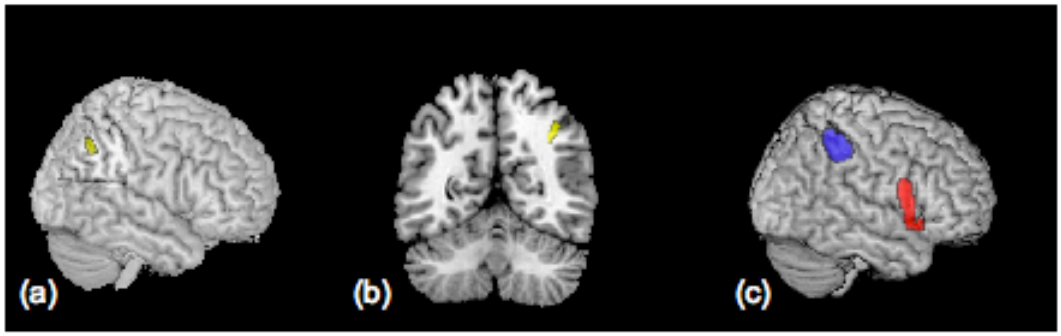


Fig 2 Behavioral and functional data. Error size for all trials (in pixels), for all four conditions are shown in (a): The largest errors were committed in the "Force-grip/color" condition 39.29 (SD=26.58) (i); slightly smaller errors were registered for the "lever-adjustment/color" condition 28.68 (SD=5.88) (ii); and force-grip/dot-on-a line" condition 32.60 (SD=10.06) (iii). The smallest errors were committed in the "lever adjustment/dot-on-a-line" condition 22.60 (SD=3.99) (iv). Error bars reflect mean ± standard error of mean. Reaction time in ms for all four conditions are depicted in (b): The shortest reaction time was found for "Force-grip/dot-on-a-line" condition 823.30 ms (SD=146.27) (i), followed by the "force-grip/color" 881.21 ms (SD=204.63) (ii) and "lever adjustment/dot-on-a-line" condition 1031.12 ms (SD=198.54) (iii). The longest RT was registered for "lever-adjustment/color" condition 1049.12 (SD=153.78) (iv). Error bars reflect ± standard error of mean. In (c) percent BOLD signal change is depicted. It was computed for the intraparietal sulcus (undulated stripes), the supramarginal gyrus (checked lines) and the PMv (vertical lines). These areas had been revealed by a conjuction analysis to be activated for all conditions "force-grip/color" (i), "lever adjustment/ color" (ii), "force-grip/dot-on-a-line" (iii) and "lever-adjustment/dot on- a-line" (iv).



Intraparietal Gyrus (d)

Visual stimulus	Instrument: Force-grip	Instrument: Lever-adjust.	Eta^2 = 0.22
Color	0.22	0.38	
DoL*	0.32	0.46	
	Eta^2 = 0.235		

Supramarginal Gyrus (e)

Visual stimulus	Instrument: Force-grip	Instrument: Lever-adjust.	Eta^2 = 0.12
Color	0.37	0.58	
DoL*	0.39	0.99	
	Eta^2 =0.265		

PMv (f)

Visual stimulus	Instrument: Force-grip	Instrument: Lever-adjust.	Eta^2 = 0.10
Color	0.28	0.35	
DoL*	0.29	0.43	
	Eta^2 =0.213		

Fig. 3 Location of ROIs which entered the effect size analysis are shown from left to right: in (a) and (b) the intraparietal sulcus and in (c) the supramarginal gyrus (in blue) and PMv (in red) is depicted. Results from the analysis of effect size are summarized in (d)-(f). Effect sizes have been
calculated for each task condition split into the two components (sensory input and motor response) for the three ROIs intraparietal gyrus (d), the supramarginal gyrus (e) and PMv.

As a further test of comparability, the task difficulty experienced was assessed by a questionnaire completed by subjects after the imaging session. Evaluation of the questionnaire revealed no significant difference in the task difficulty, as experienced by subjects (Chi-square $_3$ = 3.4, P =0 .334). Finally, no significant interaction was found for the different colors and reaction time in the context of the adapted SNARC-paradigm ($F_{1, 6}$= 0.341, P = 0.580). The possible impact of the differences in the task conditions on the neural activity will be reviewed in the discussion.

4.4.2 Imaging results

4.4.2.1 Baseline activation and conjunction analysis, four conditions

Activation of IPS and infPPC was observed during all four conditions in the sensorimotor task (Fig. 4 a-d). However, the degree of IPS and infPPC activation was different between the conditions, and appeared to depend mostly on the spatial demands of the motor act. The least IPS and infPPC activation was elicited during the “force-grip/color” condition, in which slight activation could only be seen in the

right IPS, slightly reaching into the gyrus supramarginalis. Somewhat greater and bilateral activation of IPS and inferior parietal lobule was detected in the “force-grip/dot-on-a-line” condition, whereas a dramatic increase of infPPC activation was observed in the “lever-adjustment/dot-on-a-line” condition. Highest infPPC activation was detected in the “lever-adjustment/color” condition. Spatial components of the motor task would thus appear to have more impact on the degree of infPPC activation than the visual modality. Bilateral activation of the cerebellum and visual cortex and unilateral activation of various prefrontal areas in the right hemisphere was common to all task conditions. For a more detailed description of imaging results, see Table 1.

Conjunction analysis revealed that eight clusters were involved in all four tasks. Two clusters were detected in the prefrontal cortex: one in the right ventral premotor area (PMv, BA 6/44; cluster-size: 355 voxels) and one in the anterior part of the right inferior frontal gyrus (IFG, BA 46/10; cluster-size: 315 voxels). Additionally, further common activation areas were also found in the right supramarginal gyrus (cluster-size: 360 voxels), in the lateral bank of the IPS (cluster-size: 35 voxels) and bilaterally in the cerebellum (cluster-size: 160 voxels (left), 11 voxels (right)) and occipital lobe (cluster-size: 195 voxels (left), 110 voxles (right)). Three of these areas (IPS, supramarginal gyrus and PMv) were subjected to a percent signal change analysis (Fig. 2). The two areas in the parietal cortex were chosen, since they are specifically discussed in the context of visuomotor transformation processes (Grefkes & Fink, 2005) and the PMv was chosen due to its well known involvement in motor planning due to external information (Dafotakis et al., 2008). For the IPS, the signal increased relative to baseline (null events) by 0.22% (±0.19), 0.31% (±0.21), 0.38% (±0.36), and 0.46% (±0.25) for the conditions, “Force-grip/color”, “force-grip/ dot-on-a-line”, “lever-adjustment/color”, and “lever-adjustment/dot-on-a-line” respectively. A similar picture was found for the supramarginal gyrus, where the respective values were 0.36% (SD=0.21), 0.39% (SD=0.24), 0.58% (SD=0.42) and 0.99% (SD=1.20). The same order of effect sizes was also observed in the PMv: The lowest percent signal change was found for the “Force-grip/color” condition 0.28% (SD=0.15), followed by the “force-grip/dot-on-a-line” 0.30% (SD=0.19) and “lever-adjustment/color” condition 0.35% (SD=0.27). As in the other areas the strongest percent signal change was registered for “lever-adjustment/dot-on-a-line” condition 0.43% (SD=0.18). The repeated measure within subject ANOVA revealed significant effects of the used motor instrument in the supramarginal gyrus ($F_{(1,14)}$=4.82; p = 0.046) with eta^2 = .12 and no significant effect for the visual stimulus type

($F_{(1,14)}$=1.97; p = 0.182) with eta^2= 0.256. To reduce Type 1 errors, Sidak-adjusted alpha levels were used. A trend towards greater BOLD effects of the dynamic than the isometric task was found in the lateral bank of the middle IPS ($F_{(1,14)}$=4.30; p = 0.057) with an eta^2= 0.235 but no significant effect for the visual stimulus type ($F_{1,14}$=3.91; P = 0.218) eta^2= 0.218. In the PMv area, no significant visual stimuli type ($F_{1,14}$=1.56; P = 0.1) eta^2= 0.1 or instrument ($F_{1,14}$ =3.78; P = 0.232) eta^2= 0.213 effects were detected. The determination of explained variance revealed that the factor instrument explained 55.4% and the factor visual stimuli only 24.9% of the modulation in intraparietal activity induced by our experimental manipulation. The supramarginal gyrus activity can be explained by the factor instrument to 60.8% and by the factor visual stimuli to 36.9% while the PMv activity can be explained to 33.3% by the visual stimulus and 52.0% by the instrument. In all three regions, the factor "instruments" explains more variance in the % BOLD signal change, than the factor visual information.

Contrast	Anatomical area	MNI x	MNI y	MNI z	Cluster size (# voxel)	p-value	T score
"force-grip/color" condition							
	Occipital lobe	**28**	**-100**	**-10**	**3139**	**0.001**	**14.47**
	Precentral gyrus (BA44)	**56**	**10**	**10**	**581**	**0.001**	**8.18**
	Inferior frontal gyrus (BA 10, BA 46)	**50**	**46**	**14**	**469**	**0.001**	**7.17**
	Basal Ganglia	**16**	**-4**	**6**	**289**	**0.001**	**6.08**
	Inferior parietal lobule	**52**	**-44**	**52**	**381**	**0.001**	**6.74**
"lever-adjustment/color" condition							
	Inferior parietal lobule (gyrus supramarginalis)	**52**	**-34**	**48**	**4942**	**0.001**	**12.74**
	Inferior parietal lobule (gyrus angularis)	32	-58	38			11.45
	Superior parietal lobule	48	-48	60			9.65
	Anterior parietal lobule	66	-24	25			5.80
	Inferior parietal lobule (gyrus supramarginalis)	**-66**	**-26**	**30**	**4771**	**0.001**	**6.62**
	Inferior parietal lobule (gyrus angularis)	-26	-58	40			5.49
	Intraparietal sulcus	-48	-48	56			8.54
	Anterior parietal lobule	-46	-34	64			5.35
	Precentral gyrus (BA 4)	-34	-26	66			6.71
	Occipital lobe	**30**	**-88**	**-18**	**9861**	**0.001**	**8.17**
	Insula	**40**	**2**	**-4**	**2090**	**0.001**	**5.76**
	Inferior frontal gyrus	**46**	**38**	**12**	**1265**	**0.001**	**7.03**
	Medial frontal gyrus (BA 6)	**4**	**12**	**50**	**511**	**0.001**	**6.45**

Contrast	Anatomical area	MNI x	MNI y	MNI z	Cluster size (# voxel)	p-value	T score
"force-grip/dot-on-a-line" condition							
	Inferior parietal lobule (gyrus supramarginalis)	**58**	**-30**	**34**	**2003**	**0.001**	**5.79**
	Inferior parietal lobule (gyrus angularis)	32	-56	42			10.61
	Inferior parietal lobule (gyrus supramarginalis)	**-38**	**-30**	**48**	**592**	**0.001**	**4.73**
	Precentral gyrus (BA 4)	-30	-32	54			5.12
	Insula	**32**	**20**	**2**	**1311**	**0.001**	**7.30**
	Inferior temporal gyrus	**42**	**-66**	**-16**	**275**	**0.001**	**5.24**
	Occipital lobe	**-50**	**-72**	**-8**	**753**	**0.001**	**7.10**
	Cerebellum	**4**	**-58**	**-22**	**493**	**0.001**	**5.68**
	Cerebellum	**-44**	**-62**	**-32**	**426**	**0.001**	**5.62**
	Inferior frontal gyrus	**46**	**46**	**6**	**648**	**0.001**	**5.97**
"lever-adjustment/dot-on-a-line" condition							
	Inferior parietal lobule (gyrus supramarginalis)	**54**	**-36**	**50**	**4234**	**0.001**	**11.61**
	Inferior parietal lobule (gyrus angularis)	32	-60	40			7.41
	Intraparietal sulcus	22	-78	50			4.84
	Anterior parietal lobule	58	-30	42			11.02
	Inferior parietal lobule (gyrus supramarginalis)	**-54**	**-34**	**48**	**2981**	**0.001**	**5.54**
	Inferior parietal lobule (gyrus angularis)	-38	-50	46			8.14
	Intraparietal Sulcus	-30	-70	60			6.84
	Precentral gyrus	-60	-18	48			4.38
	Occipital lobe	**32**	**-96**	**-16**	**264**	**0.001**	**7.58**
	Occipital lobe	**-52**	**-74**	**-10**	**995**	**0.001**	**8.82**
	Cerebellum	**-38**	**-62**	**-36**	**293**	**0.001**	**5.99**
	Cerebellum	**52**	**-62**	**-36**	**707**	**0.001**	**6.10**
	Inferior frontal gyrus	**48**	**10**	**14**	**4848**	**0.001**	**9.97**
	Basal Ganglia	**12**	**0**	**6**	**2373**	**0.001**	**7.01**
	Frontal medial gyrus (BA6/10)	**44**	**4**	**60**	**762**	**0.001**	**4.07**

Table 1 Anatomical specification, cluster size (#voxels), p-value for corrected cluster-level, MNI coordinates, and t-values identified for local maxima within the cluster of the four conditions (baseline activation).

Contrast	Anatomical area	MNI x	MNI y	MNI z	Cluster size (# voxel)	p-value	T score
"color" >"dot-on-a-line"							
	Primary visual cortex	**-22**	**-94**	**2**	**5685**	**0.001**	**11.60**
	Primary visual cortex	14	-86	-20			5.67
	Gyrus parahippocampalis	**-22**	**-28**	**-8**	**20**	**0.001**	**4.56**
"dot-on-a-line" > "color"							
	Inferior temporal gyrus	**-46**	**-8**	**-28**	**476**	**0.001**	**6.57**
	middle temporal gyrus	**-62**	**-62**	**2**	**429**	**0.001**	**5.68**
	Inferior temporal gyrus	**56**	**-54**	**-8**	**571**	**0.001**	**4.84**
	middle temporal gyrus	54	-56	4			5.41
	Inferior parietal lobule (gyrus supramarginalis)	**66**	**-36**	**34**	**165**	**0.001**	**5.52**
	Superior frontal gyrus	**30**	**2**	**66**	**86**	**0.001**	**5.71**
lever-adjustment device > force-grip device							
	Frontal inferior gyrus	**46**	**10**	**30**	**1093**	**0.001**	**7.35**
	Frontal middle gyrus	40	32	20			5.70
	Precuneus	**-10**	**-76**	**48**	**1856**	**0.001**	**5.20**
	Precuneus	8	-60	46			6.56
	Cuneus	-4	-82	36			4.64
	Cuneus	12	-72	36			4.83
	Inferior parietal lobe	-44	-52	46			5.73
	Superior parietal lobe	-24	-74	58			5.54
	Inferior parietal lobe	**38**	**-50**	**44**	**2992**	**0.001**	**6.27**
	Superior parietal lobe	30	-52	64			4.05
	Anterior parietal lobe	58	-24	54			5.41
	Middle frontal gyrus (BA6,9)	**-48**	**0**	**26**	**495**	**0.001**	**6.44**
	Posterior temporal lobe	**62**	**-48**	**-18**	**417**	**0.001**	**5.66**
	Middle frontal gyrus	**40**	**-4**	**54**	**1158**	**0.001**	**4.00**
	Superior frontal gyrus	24	-4	74			5.39
force-grip device > lever-adjustment device							
	-	-	-	-	-	-	-

Table 2 Anatomical specification, cluster size (#voxels), p-value for corrected cluster-level, MNI coordinates, and t-values identified for local maxima within the cluster of the four contrasts.

4.4.2.2 Dynamic vs. isometric movements contrasted

Contrasts between lever-adjustment and force-grip instrument were calculated to identify the neural network specific to dynamic motor responses compared with isometric motor response (anatomical locations are summarized in Table 2). Six activation clusters were evident in this direct contrast (Fig. 4 (e)). Three clusters were located in the prefrontal cortex, including the right inferior (BA6/44), middle (BA45/10), and superior frontal gyrus (BA4/6) and the left middle frontal gyrus (BA6/9). Two additional clusters were revealed in the parietal cortex, one in the medial wall (cuneus and precuneus) and one in the depth of the IPS, expanding from middle to the caudal part and covering the medial and lateral wall. An activation cluster was found also in the posterior temporal lobe. Activation predominantly occurred in the right hemisphere. Since no activation was found by calculating the reverse contrast (non-spatial vs. spatial movement), the discussion focuses on the contrast between dynamic and isometric motor acts.

4.4.2.3 Spatial and non-spatial visual information contrasted

The direct contrast between “dot-on-a-line” and “color” was calculated to define the neural network specific to visual stimuli requiring spatial judgment compared to visual stimuli requiring no spatial judgment (Fig.4(f)). The contrast revealed increased bilateral activation in the inferior and middle temporal gyrus as well as in the right inferior parietal lobe (marginal gyrus) and right superior frontal gyrus. In the contrast between “color” and “dot-on-a-line”, activation was only found bilaterally in the primary visual cortex.

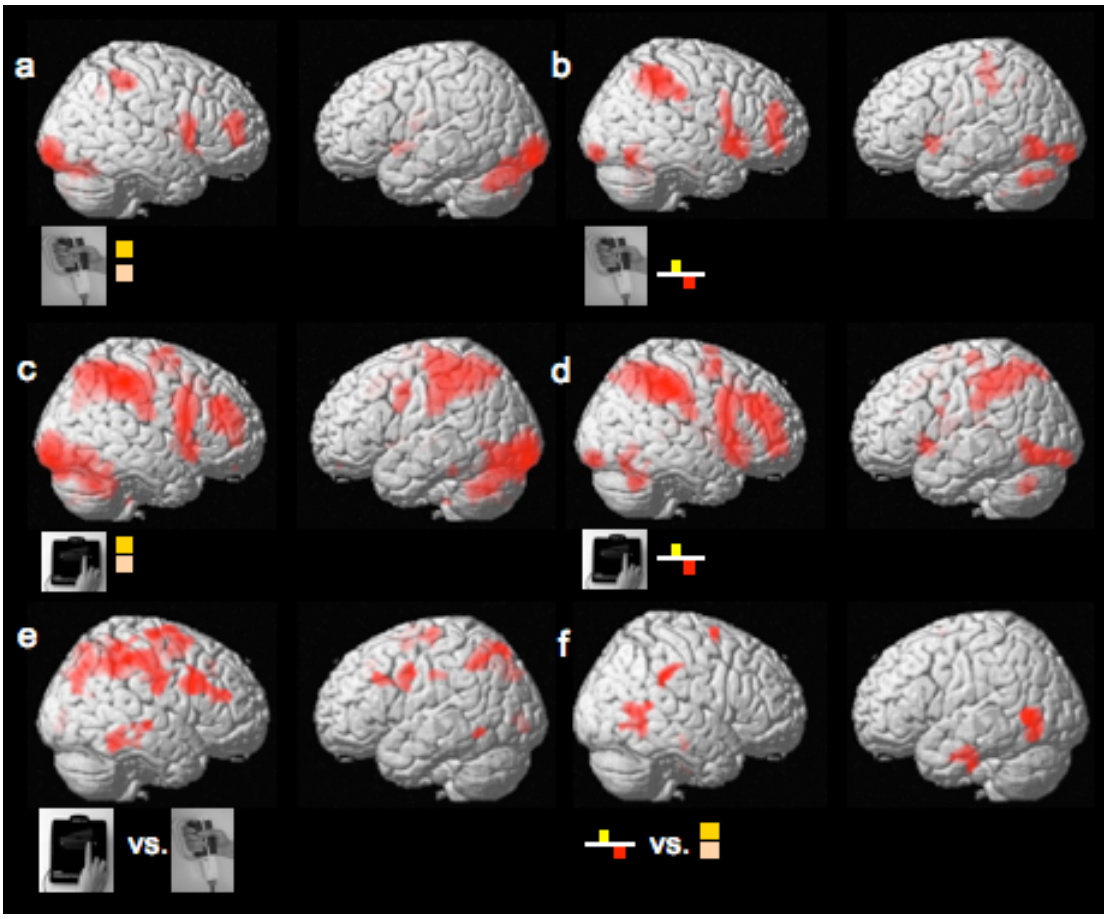


Fig. 4 Imaging data. Anatomical location (SPM (t) s of the baseline activation (a)-(d) of the four conditions detailed in Table 1, overlaid on spatially normalized MNI single-subject brain) and parameter estimates (+/- 90% confidence interval boundary) for the (a) “force-grip/color” condition, (b) “force-grip/dot-on-a-line” condition, (c) “lever-adjustment/color” condition and (d) “lever-adjustment/dot-on-a-line” condition. (e) and (f) depict the contrast detailed in Table 2 for (a) “all lever-adjustment” vs. “all force grip” (spatial vs. non spatial movement) and (b) “all dot-on-a-line” vs. “all color” (spatial vs. non spatial visual information).

4.5 Discussion

The aim of this study was to investigate the neural correlates of sensorimotor transformation tasks in which the spatial requirements of the motor response and of the visual instruction cues were systematically varied. The visual stimuli consisted of a colored square (no spatial judgment necessary) in two of the conditions and of a line with a dot above (spatial judgment necessary) in the other two conditions. In all conditions, the visual stimulus had to be followed by a dynamic motor response (limb coordination in space) or an isometric motor response (no limb coordination in space).

Firstly, as expected, we found IPS and infPPC to be activated in all four task conditions. Secondly, we found only a small difference in infPPC activity restricted to the marginal gyrus for the visual stimuli dependent on spatial content. And finally, we found that dynamic movements activate the IPS and the infPPC to a much bigger extent than isometric movements.

4.5.1 Activity common to all four task conditions

Conjunction analysis revealed IPS, infPPC, motor and prefrontal areas to be activated in all four conditions. These areas have all been linked to the sensorimotor network and our results are in line with previous work (e.g. Toni et al., 2001a; Floyer-Lea & Matthews, 2004; Imamizu et al., 2007).

The parietal lobe can be defined as the area posterior to the primary somatosensory areas, superior to the lateral and anterior to the parieto-occipital sulcus. It can be subdivided into the superior and interior parietal lobule with the two separated by the IPS. Especially the IPS plays a dominant role in sensorimotor transformations, and the areas within the IPS serve as interfaces between the perceptive and motor system for planning, executing and monitoring motor responses (Grefkes & Fink, 2005). Anatomically, these areas are interconnected and Stark and Zohary (2008) reported two opposite gradients in the IPS: The involvement of IPS decreases from anterior to posterior for the analysis of visual-field information and increases for movement planning. Our analysis revealed that more than 50% of the IPS activity we found can be explained by the motor response and only 25% by the sensory stimuli. From this we conclude that motor response type has a greater impact on brain activity than does the type of visual stimulus.

In addition to the IPS, we found activity in the infPPC. The infPPC can be divided into two parts, the angular (BA 39) and supramarginal gyrus (BA 40) (Gruber and Zenker 1994) and as in the IPS, activity in the infPPC is explained to a larger degree by the motor than by the sensory part. From an anatomical point of view, the IPS and the infPPC are well suited for integrating input and output information during sensorimotor tasks, since they receive information from somatosensory areas and are connected to ventral and dorsal premotor areas (Tanne et al., 1995; Jancke, 2007). The infPPC is traditionally associated with the dorsal visual stream, a site responsible for integration of visual input to motor output (Goodale & Milner, 1992) but lately this view has been specified by Rizzolatti and Matelli (2003). They claim that the dorsal stream should be divided into two substreams, namely a dorso-dorsal

(supPPC) and a ventro-dorsal substream (infPPC). While the former is engaged in online monitoring, the latter is involved in cognitive aspects of movement planning such as the formation of intentions (Pisella et al., 2006), and is responsible for the planning of movements (Mars et al., 2007), motor learning tasks (Toni et al., 2001a), and the early-onset planning of future motor actions (Andersen & Buneo, 2002; Buneo & Andersen, 2006). In fact, electrophysiological studies provide direct evidence for the involvement of infPPC in an early stage of motor planning (Duhamel et al., 1992). Taken together, our results match previous results. However, detailed analysis of the activation patterns associated with each condition reveals several differences in the degree of IPS and infPPC activation. The baseline contrast of the *"force-grip/color"* condition revealed significant activation only in the IPS of the right hemisphere, while activation of both IPS and infPPC occurred bilaterally in the other three conditions.

4.5.2 Dynamic and isometric movements have a different impact on infPPC activity

To define the neural correlates specific to dynamic in contrast to isometric motor responses these two motor response types were contrasted with each other. The main "motor response" effect revealed a parieto-frontal network, with a right-sided dominance in favor of the motor response demanding a dynamic manipulation. We found bilateral prefrontal, cuneus and precuneus, infPPC and supPPC as well as right IPS activity to be more dominant in the condition in which a visual stimulus had to be transformed into a dynamic movement vs. an isometric movement. We argue that this increased activation in the IPS, the infPPC and pre-motor cortex is the result of increased demand on muscle coordination: more than just the one agonist/antagonist pair have to be recruited to manipulate the lever-adjustment instrument. This increased demand on muscle coordination is most likely to rely on a more complex level of planning and programming, which activates the infPPC more vigorously in return. These results support a thesis by Rizzolatti and Matelli (Rizzolatti & Matelli, 2003), which suggests that the infPPC is involved in the perception and organization of motor activities. An increase in parieto-frontal network activity with an increased complexity in motor activity has also been reported by Wexler (1997) Gordon (1998) and Harrington and colleagues (2000). They reported on neural activity in tasks in which the influence of the number of fingers involved was investigated.

The difference in activation between dynamic and isometric motor responses is especially predominant in the IPS. It covered the fundus (hVIP) as well the lateral (hLIP) and medial (hMIP) wall and expanded from the middle to the caudal part of the IPS. The hVIP constitutes a polymodal association zone, which receives projections from motor, sensorimotor, auditory and several visual areas (Klam & Graf, 2003), and the hMIT neurons are crucial for transforming visual coordinates into motor responses and controlling of goal-directed precision movement (Grefkes et al., 2004). Also electrophysiological studies in macaques have shown that MIT neurons are involved in planning, executing and monitoring of outcome of movements, are part of the parietal reaching region (Cohen & Andersen, 2002) and that their discharge rate is dependent on the direction of hand movement executed on a joystick. Additionally, behavioral data also showed significantly longer reaction times for dynamic movements, which indicates that these kinds of movements rely on a more complex level of planning. Taken together we claim that these enhanced parieto-frontal activations are the result of complex a- and antagonist interaction on muscular level.

4.5.2.1 Spatial vs. color visual information elicits activity in the supramarginal gyrus

As expected, we found enhanced infPPC activity in the condition requiring spatial judgment than in the condition requiring none. This result is consistent with the dorsal stream theory, which states that the dorsal stream is involved in the analysis of the spatial attributes of visual stimuli (Ungerleider and Mishkin 1982). Lesions in the dorsal stream lead to severe spatial deficits, e.g. spatial neglect (Ungerleider & Mishkin, 1982). Patients with right infPPC lesions do not pay attention to objects presented to the contralesional side, or they can still perceive objects but not identify their locations (Vallar, 2007). Further, infPPC activation has also been reported for tasks in which subjects had to make spatial judgments (Pinel et al., 2004; Kleinschmidt, 2004; Stephan et al., 2007). Hazeltine and colleagues (1997) compared part of their new data on non-spatial visual stimuli with data on spatial visual stimuli from an earlier study (Grafton & Hazeltine 1995). This comparison concerned the spatial vs. non-spatial properties of the visual information in otherwise mostly comparable visuomotor tasks. For the spatial vs. non-spatial information, they found activation in the occipital, the inferior parietal lobule and in the frontal areas, while we mainly find activation in the supramarginal gyrus and the frontal and temporal lobe. These obvious discrepancies between Hazeltine's study and our own might be due in part to differences in the method of investigating brain activity. In this

study, we used fMRI and compared two conditions, while Hazeltine and colleagues used PET to compare the results of two different studies measured using different subjects. Furthermore, our task was based on continuous manipulation, whereas their PET study investigated discrete movements. Another possible reason for the observed differences could be the properties of color-coded stimuli: While Hazeltine and colleagues's stimuli were limited to four discrete colors, our visual stimuli comprised a quasi continuous color spectrum. Further studies are required to resolve these discrepancies.

Surprisingly, additional temporal cortex activation was revealed in the spatial- vs. color information contrast. This is somewhat unexpected since the temporal lobe is part of the ventral steam (Ungerleider & Mishkin, 1982), which has long been thought to be involved in the analysis of form, color and identity of objects. The additional temporal activation found in our study might be explained by Biederman's theory (Biederman, 1987), which states that objects are analyzed according to their basic component parts, the so-called geometric icons (geons). The temporal lobe activation in this contrast can thus be explained by the fact that the spatial visual information contains more geons than the non-spatial visual information. The non-spatial visual information contains two geons (two quadrants), while the spatial visual information contains at least three geons (two quadrants and one line). A higher number of basic elements might therefore increase the complexity of an object, and this increased complexity could, in turn, be the source of the unexpected additional activation in the temporal cortex.

4.5.3 The type of motor response has a greater impact on IPS and infPPC than the type of spatial component on the sensory side

Supported by results contrasting the processing of spatial components with non-spatial components on the motor side, we state that the spatial component of motor action has a great impact on the strength and extent of infPPC activity. While non-spatial movements activate only the IPS, with slight spread into the inferior part of the parietal cortex, spatial movements activate the IPS and major parts of the infPPC. On the other hand the contrast between "spatial" and "color" visual information reveals only a slight difference in infPPC activation, and this is restricted to the right supramarginal gyrus. From this we conclude that spatial components of the motor effect have greater impact on IPS and infPPC activity than do spatial components of sensory stimuli.

To interpret the results obtained in this study correctly, several potential caveats and limitations inherent to the applied paradigm need to be taken into account. Despite the overall correspondence between the stimuli and responses used in the four conditions, it might be argued that some of our results could be explained by residual sensory or motor-related discrepancies, rather than by differences in the visuomotor transformation processes evoked by the four task conditions. For example, one could argue that the observed influence of instrument manipulation on infPPC activity could be attributed to variability in the overall applied force, instead of spatial properties. In order to control for the effect of force variability, a parametric analysis of BOLD responses was applied during the isometric handgrip condition, with force as a modulatory parameter. This analysis revealed activation in the somatosensory cortex related to strength, as usually reported by force coding studies (Thickbroom et al., 1998; Cramer et al., 2002), but no indication that infPPC activity covaried with the force applied to the force-grip device. Thus, the amount of force applied to the device is unlikely to be causally related to differential infPPC activity.

Reaction time varied significantly different between the conditions. Reaction time differences may be due to greater demands on visuomotor transformation when the motor action has to be coordinated in space, or they may be due to low-level mechanical factors when handling a lever. Since a control experiment in which no visual goal was presented revealed comparable reaction time differences for both kinds of motor responses, we conclude that reaction time differences are not due to the influence of low-level mechanical factors. The difference of reaction time could be attributed to unequal planning and motor demands from the two instruments. A parametric analysis control for reaction time was carried out to find out whether this difference had an impact on the infPPC activity. This revealed activation increase in the cuneus and angular gyrus with longer reaction time. The reaction time might be influenced by the variable number of muscles involved in movement execution. In our case, the number of muscles needed for the lever adjustment task is different from that in the grip force task, in that more muscles are recruited for dynamic movement. The activation of more muscles might underlie increased activation in the infPPC. In turn, this is likely to reflect additional planning steps, and greater activation of motor areas (due to higher demands from coordinating muscle groups). In this context, we have to consider, whether the coordination of different muscle groups is different in principle from the coordination of movements in space. Presenting the case of this experiment, we argue that *because* movements had to be spatially organized, multiple muscles (agonist and antagonist) had to be coordinated in the one condition.

In the other condition, such coordination was not necessary, so the movement could rely on fewer muscle groups. Nevertheless, we cannot exclude situations in which the coordination of multiple muscle groups may be unrelated to coordination in space. Such situations will require special investigation in order to settle the question of whether infPPC activity found in this study is related to the coordination of muscle groups but not to coordination of movements in space. In addition to these factors, supplementary activation in the prefrontal areas due to elevated complexity of movement and a greater need for cognitive control might also increase computational demands, resulting in longer reaction time in turn.

A further caveat concerns saccades and their potential contribution to IPS activity. The lateral part of the IPS receives input from several visual areas, is interconnected with the frontal eyes field, and mediates saccades (Fink et al., 1997). Since eye movements have not been controlled for, it cannot completely be ruled out that they might have caused some additional activity in the parietal cortex.

Finally, it could be argued that the colors used as sensory cues might be mentally represented as a continuum and therefore contain spatial information. To exclude this potentially confounding aspect, we controlled the mental representation of this color range with an adapted version of the SNARC-paradigm (Dehaene et al., 1993). Since no significant interaction between color and reaction time was found, we conclude that this color range is not mentally presented in such a way that it encodes spatial elements.

4.5.4 Conclusion

The goals of the study were to establish (1) which brain areas are responsible for coordination of movements in space and (2) whether there are structures shared for analysis of visuospatial analysis in the context of visuomotor integration. Therefore, a sensorimotor transformation task was applied in which these tasks were systematically varied. We found that dynamic movements were associated with significantly greater infPPC and IPS activation than isometric motor responses. This finding can be attributed to the need of more coordination of muscle groups for dynamic compared with isometric movements. In contrast to the important difference in infPPC activity between the two kinds of motor responses, spatial judgment of the visual stimuli in the context of visuomotor integration evoked activation differences only in supramarginal gyrus. In areas which were commonly activated by both (visual and motor) spatial tasks, the spatial load of motor coordination had a stronger influence on BOLD signal than the spatial load of the visual stimulus.

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5. Study 2

Motor and non-motor error and the influence of error magnitude on brain activity

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5.1 Abstract

It has been shown that frontal cortical areas increase their activity during error perception and error processing. However, it is not yet clear whether perception of motor errors is processed in the same frontal areas as perception of errors in cognitive tasks. It is also unclear whether brain activity level is influenced by the magnitude of error. For this purpose, we conducted a study in which subjects were confronted with motor and non-motor errors, and had them perform a sensorimotor transformation task in which they were likely to commit motor errors of different magnitudes (*internal errors*). In addition to the internally committed motor errors, non-motor errors (*external errors*) were added to the feedback in some trials. We found that activity in the anterior insula, inferior frontal gyrus (IFG), cerebellum, precuneus, and posterior medial frontal cortex (pMFC) correlated positively with the magnitude of *external errors*. The middle frontal gyrus (MFG) and the pMFC cortex correlated positively with the magnitude of the *total error* fed back to subjects (*internal plus external*). No significant positive correlation between *internal error* and brain activity could be detected. These results indicate that motor errors have a differential effect on brain activity compared with non-motor errors.

5.2 Introduction

Imagine yourself playing tennis. You throw the ball into the air, hit the ball and observe where it hits the ground. Throwing the ball, hitting it and monitoring the consequences are typical components of sensorimotor transformation tasks. The ball may hit the ground exactly where you wanted it to, although other outcomes also are possible. The ball may hit the ground right next to the planned spot, or could hit the ground way off the mark. There are several possible causes for such misses. A failure in precision may be due to an inappropriate movement by the agent. Alternatively, the ball's flight trajectory may have been changed (e.g. by a squall)

even though the executed movement may have been fully appropriate. In the first case the cause of the failure lies with the agent (self caused error, from now on called "*internal error*"), while in the second case, the cause lies with the agent's environment (externally caused error, from now on called "*external error*"). In most real-world situations, however, the failure will be due to a mixture of both, say a suboptimal motor action plus an additional external distortion. In any case of an error, by definition the intended goal does not agree with the achieved state.

The capacity to detect errors, i.e. to compare intended with actual outcome has been termed *error* or *performance monitoring* (Botvinick et al., 2001) and its neural correlates have received great attention in cognitive neuroscience. Studies on error detection in cognitive tasks (e.g. flanker tasks) have consistently reported activation of prefrontal areas, subcortical structures and parietal structures, with the anterior cingulate cortex and posterior medial frontal cortex (pMFC) playing the major role (Ridderinkhof et al., 2004; Nachev et al., 2007) . The pMFC seems not only to be involved in monitoring of *internal* non-motor errors (Botvinick et al., 2001; Ullsperger & von Cramon 2001; Fiehler et al., 2004; Li et al., 2008), but also in tasks in which the errors have *external* causes (Holroyd et al., 2004; Ullsperger et al., 2007). In addtion to this the pMFC is involved in signaling the need for behavioral adjustments (Kerns et al., 2004; Ullsperger & von Cramon, 2004). Meanwhile, researchers investigating motor errors have focused on the cerebellum and the parietal cortex (Blakemore et al., 2001; Blakemore, 2003; Imamizu et al., 2003; Imamizu et al., 2004) and have suggested the concept of internal models. These internal models consist of two parts, an inverse and a forward model. While the forward model makes predictions about the behavior of the motor system and its sensory consequences, the inverse model calculates the motor commands required to achieve a certain goal. Deviations from the predicted and the actual outcome are detected by the forward model and used to update motor commands (Wolpert et al., 1995; Wolpert & Kawato, 1998; Kawato, 1999; Imamizu et al., 2007).

In the present fMRI study, we investigated perception of errors caused by an agent's motor system and errors caused by environmental factors, thereby considering how error magnitude impacts brain activity. To investigate these factors, we arranged for subjects to perform a sensorimotor transformation task in which they were likely to commit motor errors of different magnitudes; in some trials they were given incorrect feedback about their performance. In view of the pertinent literature, we anticipate activation in the pMFC to correlate with magnitude of *internal* and *total error*, as

these error types reflect a general mismatch between the intended and actual outcome. Specifically for *external error* we expect cerebellar and parietal activity to correlate with their magnitude, because these *external errors* cannot be predicted by the forward model and the therefore there is a mismatch between expected and actual outcome - the higher the mismatch the stronger the need to update the internal model.

5.3 Materials and Methods

5.3.1 Participants

Seventeen healthy right-handed subjects (24.5 years, SD: 3.2, 10 males), whose handedness was assessed with the Annett Handedness-Questionnaire (Annett, 1970), participated in this study. Subjects gave written informed consent and performed two scanning runs, which were separated by a short break (1-2 min). They were naïve about the purpose of the experiment and received 30 CHF for participation (approximately 30 US Dollars). The study was approved by the local ethics committee and tasks and testing procedures were in accordance with institutional guidelines of the Helsinki Declaration.

5.3.2 Stimuli and apparatus

At the beginning of each trial a yellow square (visual angle of approximately 0.1°) was presented above a horizontal line (visual angle of approx. 14°) as a target cue (Fig. 1a). Its left-right position indicated the strength to be applied to a force-grip device (see below). The position of each target square was randomly chosen before the experiment from the full range of possible positions without repetitions. After the movement, a red square (visual angle of approximately 0.1°) was presented below the line as feedback. Feedback cues were placed according to the subjects' action. In 35% of the trials, their left-right position was additionally displaced (Fig. 1b). The motor responses were recorded with an MRI-compatible isometric force-grip device (isometric Sensory-Motor Systems Laboratory, ETH Zurich and University of Zurich), which was set to measure isometric grip force with a frequency of 60Hz from 0 to 40N in 8bit resolution.

5.3.3 Task

The task consisted of a sensorimotor transformation. Sensorimotor transformations are usually characterized by a certain relationship between sensory stimuli and motor responses. The required association between a visual stimulus and a motor response was set up according to previous experiments (e.g. by Toni et al., 2001a; Toni et al., 2001b), with the difference that the motor response consisted of a quasi-continuously graded application of force on a force-grip device (Floyer-Lea & Matthews, 2004; Floyer-Lea & Matthews, 2005; Keisker et al., 2009). In our experiment, the subject had to apply a force on a force-grip device as indicated by the target cue, and minimize the difference between the positions of feedback and target cues. The force applied by the subjects on each trial was transformed into a position on the horizontal line as follows: forces less than 10N were coded by the leftmost position, whereas forces larger than 40N were translated into the rightmost position on the line. Between 10N and 40N, forces were transformed linearly into a corresponding position on the line.

In each trial, subjects were first shown the target position (square). They were instructed to apply a force that matched the target position to the force-grip device immediately after target presentation. The force applied was translated into a position along the horizontal line. Feedback triangles were always shown below the line. The spatial distance between the square and the triangle was regarded as the motor error (Fig. 1a). The motor response required manipulation of the force-grip device and it was extremely unlikely that no *internal* motor errors would have been made, i.e., that the subject attained the desired position with a deviation of less than a pixel. After presentation of the feedback, a written instruction was presented to remove force from the dynamometer and a new trial subsequently began. Each trial lasted approximately 7 sec., slightly varying due to the differing times it took for the subjects to release pressure from the force-grip device. The target cue was presented for 1.5 sec., feedback presentation lasted for 3 sec. and the request to release pressure was shown for 1.5 sec. The whole experiment consisted of 280 trials, presented in two runs of 140 trials, adding up to a total duration of approximately 35 min. The presentation times for cue and feedback were kept constant in both the correct and incorrect feedback conditions (see below) and no measures were taken to delay motor response with respect to stimulus presentation. This approach was chosen because we were not interested in disentangling the discrete steps, but focused instead on the processing of errors. Regarding the trial as a whole allowed us to increase the number of trials in favor of statistical power, to compare trials with

respect to presence or absence of *external errors* and to parametrically analyze the impact of error magnitude.

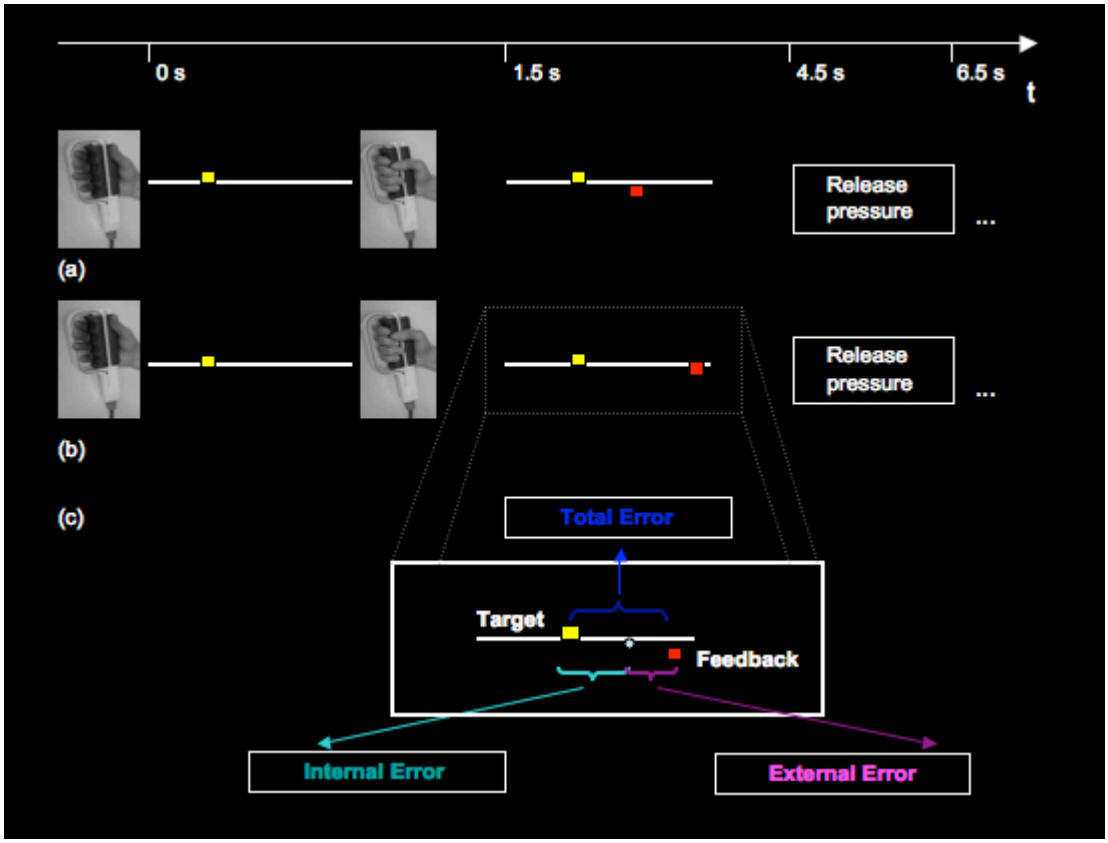

Fig. 1 Task setup. During the scanning session, participants had to associate a visual stimulus (position of a square above a line) with a motor response (application of force on the force-grip device) by trial and error. In each trial, a target square was presented above the line.
After the target cue was presented, subjects had to manipulate the force-grip device in order to evoke a force that matched the target's position on the line. After 1.5 seconds they were given visual feedback about their performance. This took the form of a feedback red square appearing at the location below the line, matching their applied force. The distance between the yellow and red square was regarded as the motor error; the closer, the better the subjects' motor performance. The fMRI-experiment consisted of two sessions, each consisting of 140 trials, in which subjects were presented with incorrect feedback in 35% of the trials. Example (a) shows a correct feedback trial, i.e. a trial in which the discrepancy between the square and triangle reflects the subjects' performance error alone (internal error). Example (b) shows an incorrect feedback trial. Again, subjects were only presented with the triangle as feedback of their performance and they were left naïve about the additional error component which had been added to the feedback. Adding an external error always increased the incorrect trial feedback error in comparison with the subjects' real motor error. After presentation of the visual feedback, a further new trial was started. Example (c) illustrates the three measures that were subjected to a parametric analysis. The gray circle is inserted to illustrate the principle and reflects subjects' performance. "Internal error" refers to the errors caused by the subject, "External error" refers to the externally added error and "Total error" describes the error fed back to subjects. This "Total error" is either the result of internal errors only (65%) or internal and external errors together (35%).

In 35% of all trials the feedback was distorted. This involved the addition of a variable extra displacement (*external error*) to the feedback position. Importantly, in order to prevent *interna*l and *external errors* from canceling each other out, we ensured that the external *error* always moved the feedback further away from the target. Thus, if the *internal* error was caused by the application of too little force (feedback square left of the cue), a further displacement to the left was added. If the *internal error* was caused by too much force (feedback square right of the cue), the *external error* was added to the right side.

The magnitude of the additional external displacement errors were randomly taken from the pool of the ten *internal errors* previously committed by the same subject. This ensured that the size of the *external errors* was adjusted to the individual performance level, and thus *external* and *internal errors* were comparable in magnitude. The occurrence of an *external error* could not be predicted and the magnitude of the added *external errors* did not correlate with the magnitude of the *internal errors*. Subjects had not been informed about the existence of incorrect feedback trials and were naïve with regard to this experimental manipulation. Prior to the fMRI scanning session, the participants performed a training session including 50 trials, during which no *external errors* were added to the feedback. This permitted them to become familiar with the task and with the use of the force-grip device, and served to stabilize performance. More importantly, this allowed an internal model to build up, which enabled the subjects to predict the position where the feedback square was to be expected according to their dynamometer manipulation.

5.3.4 Experimental setup

Throughout both scanning runs, participants lay supine in the scanner. Head movement was minimized using an adjustable vacuum cushion. Visual stimuli were projected onto a mirror above the participants' heads. The force-grip device was placed in their right hand. Stimulus presentation and response collection were controlled by *Presentation 11.2* software (Neurobehavioral Systems, Inc, Albany, USA). After the experiment, subjects were asked to complete a questionnaire in which they answered questions concerning their thoughts and emotions during the experiment and if they had noticed anything peculiar.

5.3.5 FMRI data acquisition

Functional magnetic resonance imaging was performed at the University Hospital of Zurich on a Philips Achieva 3-T whole-body MRI system (Philips Medical Systems, Best, The Netherlands). Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted three-dimensional spoiled gradient echo pulse sequence (180 slices, TR = 20 ms, TE = 2.3 ms, flip angle = 20°, FOV = 220 mm × 220 mm x 135 mm, matrix size = 224 x 187, voxel size = 0.98 mm × 1.18 mm × 0.75 mm, re-sliced to 0.86 mm x 0.86 mm x 0.75 mm). Functional data were obtained in 400 scans per run using 33 transverse slices covering the whole brain in oblique orientation. Slices were acquired in interleaved order, using a sensitivity encoded (SENSE, factor 2.0), single-shot echo planar imaging technique (repetition time, TR = 2.5 s; echo time, TE = 35 ms; field of view = 220 mm × 220 mm × 132 mm; flip angle = 78°; matrix size = 80 × 80; voxel size = 2.75 mm × 2.75 mm × 4 mm, re-sliced to 1.72 mm x 1.72 mm x 4 mm). Three dummy scans were acquired at the beginning of each run and discarded in order to establish a steady state in T1 relaxation for all functional scans.

5.3.6 fMRI data analysis

Data analysis was performed using MATLAB 7.4.0 (Mathworks Inc., Natiek, MA, USA) and SPM5 (http://fil.ion.ucl.ac.uk/spm). All images were realigned to the first recorded volume, normalized into standard stereotactical space (using the EPI-template provided by the Montreal Neurological Institute, MNI brain), re-sliced to 2 mm × 2 mm × 2 mm voxel size and smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel.

The GLM model contained eleven regressors: four for the correct feedback trials, five regressors for the incorrect feedback trials, and two additional regressors common to both feedback conditions. The first regressor for correct feedback trials was motor preparation, which was modeled as an epoch starting from target stimulus onset and lasting until the onset of the movement. Thus, the duration of this epoch was variable from trial to trial. A second regressor was an event at the onset of the motor response. The third regressor was a 1.5 s epoch starting at the onset of feedback presentation. The fourth regressor was a parametric modulation of the feedback regressor by the magnitude of *internal error* (Buchel & Friston 1998; Buchel et al., 1998) The incorrect feedback trials had the same four regressors plus an additional regressor consisting of a parametric modulation of the feedback by *external error*. Both *internal* and *external errors* were defined as the deviation (in pixels) between target and feedback. In the following, the term *internal errors* will refer to the results

of a parametric analysis of the magnitude of internally-caused error in trials where no additional external distortion was added. The term *external error* labels the results of the parametric analysis of the magnitude of externally-added errors in trials with additional external distortion. Finally the term *total error* describes the sum of responses (parameter estimates) to *internal* and *external* errors in trials with both *internal* and *external* error (Fig. 2c). Finally, the two additional regressors we used were: The first was a regressor applied to both correct and incorrect feedback trials for the instruction to release the force of grip that consisted of a 1.5 s epoch beginning with the onset of the instruction. The second was an epoch of 7 s that modeled the missed trials.

Functional data were analyzed using a general linear model involving the abovementioned 11 regressors and a high-pass filter with a cut-off period of 128 seconds. The GLM was computed for each subject and then subjected to a second-level analysis. First-level linear contrasts (against global mean) were employed to test for specific condition effects for each voxel and each subject and condition (Friston et al., 1995). This results in one statistical parametric map for each subject and each contrast (three contrasts): 1) parametric modulation by *internal error* in correct feedback trials, 2) parametric modulation by *external error* in incorrect feedback trials 3) parametric modulation by *total error* in incorrect feedback trials. These contrast images were smoothed using an 8 mm full width at half maximum (FWHM) Gaussian kernel, leading to an overall smoothing by 10 mm FWHM ((6^2+8^2)^(1/2)). This was undertaken to account for differences in intersubject localization of activated brain regions and to further increase statistical sensitivity by reducing the effective number of independent observations. In order to permit population-level inferences to be made, maps of contrast coefficients were collectively submitted to one-sample t-tests against the null hypothesis of no activation for each of the first level contrasts, while controlling for random effects. Activation differences were tested on a cluster level corrected for multiple comparisons using a statistical threshold of $p < 0.005$ and were reported using a cluster size of > 25.

5.4 Results

5.4.1 Behavioral results

Every subject performed 280 trials. Two participants were excluded from the analyses due to more than 15% missed trials, which makes them outliers with

respect to task processing. The final sample comprised 15 participants (mean age: 24.5 years, SD: 3.2, 10 male). On average, these subjects missed 12.3 trials (SD = 4.68, range: 5-20) where no action on the force-grip device took place. The average *internally-generated error* magnitude was 78.84 pixels (SD = 15.0, range: 1- 480) and the average *externally-added error* was 78.33 pixels (SD = 13.97, range: 1- 435). A two-tailed paired t-test revealed no significant difference in magnitude of motor error ($t(14) = 0.20$; $p = 0.85$)) for the correct and incorrect feedback trials. To identify whether subjects' performance changed over time, *internal error* magnitude was compared in the first and second half of the experiment using a paired t-test. This revealed no significant difference between the first and second run ($t = 0.941$, $df = 134$, $p = 0.35$).

To check for post-error-adjustment, we calculated the correlation coefficient between the errors and the following force production per subject in four different ways: (C1) Correlation of the magnitude of *internal error* with the magnitude of *internal error* of the following trial; (C2) Correlation of *total error* magnitude (*interna*l plus *external*) with *internal error magnitude* of the following trial; (C3) Correlation of *externally added error* with the *internal error* of the following trial; (C4) In order to assess any potential effect of time on this correlation we computed a correlation between *external error* and the *internal error* of the next trial (equivalent to C3) only for the first half of the dataset. No significant correlations were found between the error magnitude and the correction in the subsequent trials, suggesting that no post-error adjustment took place during the experiment.

Data from the post-experimental questionnaire revealed that 14 of 15 subjects had gained the impression that the force-grip device was sometimes not acting in the way they had intended.

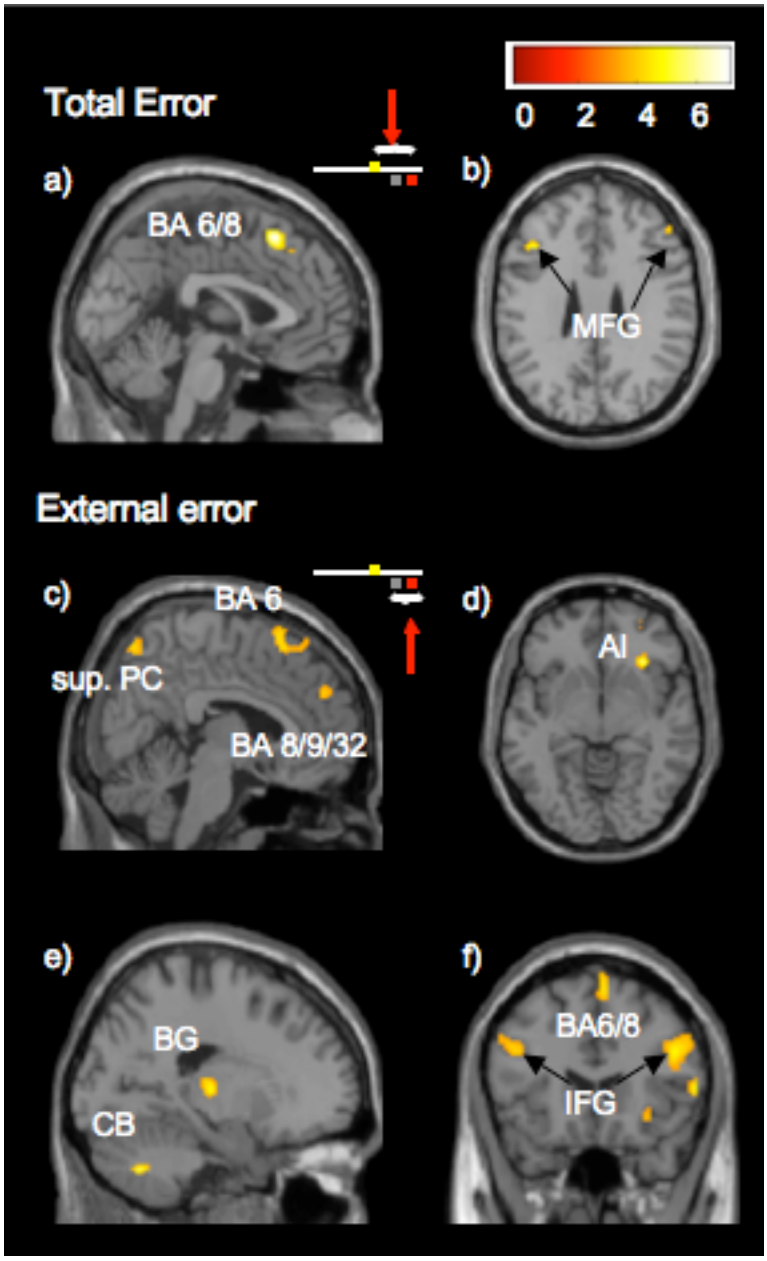

Fig. 2 Imaging Data. Anatomical location SPM(t) of the parametric analysis activations (a-e) detailed in Table 2 and 3, overlaid on an MNI standard brain, together with parameter estimates (+/- 90% confidence intervals). Images (a) and (b) depict foci in which a BOLD response is correlated with the size of total error. One area is located in the pMFC, while the two others are located bilaterally in the MFG. In contrast, images (c-f) show the areas in which a BOLD signal is correlated with the size of external error. (c) displays activity in the pMFC and sup-PC. (d) shows the ventral anterior insula (AI) and (e)
demonstrates the BG and the CB. Finally, (f) illustrates bilateral IFG and pMFC activity. pMFC: posterior medial frontal cortex; MFG: middle frontal gyrus; sup-PC: superior parietal cortex; AI: anterior insula; BG: basal ganglia; CB: cerebellum.

5.4.2 Imaging Results

First, we looked for brain regional brain activity that correlated linearly with the *total error* fed back to the subject (combined *internal* and *external*), taking all trials into account (Fig. 2 a-b, table 1). We found activity at the upper border of the rostral cingulate zone expanding into the pre-SMA, as well activity in the right and left medial frontal gyrus (MFG) to positively correlate with the *total error* magnitude. Next, we investigated whether activity in any region displayed a linear parametric modulation with the magnitude of *internal errors*. No region could be identified showing this relationship. Last we looked for regions in which activity increased linearly with the size of the *externally added error*. This analysis revealed nine clusters that showed such a relationship (Fig. 2 c-f, table 2). One of these clusters contained several local maxima. The strongest local maximum was found to be located in the right inferior frontal sulcus, the second in the right inferior frontal gyrus (IFG) and the third in the right ventral anterior insula. Left IFG/sulcus activity was also revealed. In addition, significant activation was also found in the pMFC, the left inferior semilunar lobule of the cerebellum, the MFG, the basal ganglia and in the right precuneus.

Correlation	Anatomical area	MNI			Cluster size (# voxel)	p-value	T score
		x	y	z			
Parametric analysis of total error – positive correlation							
	Posterior medial frontal cortex; BA 6, 8	**0**	**22**	**54**	**212**	**<0.001**	**7.07**
	Middle frontal gyrus	**-42**	**26**	**32**	**62**	**<0.001**	**6.28**
	Middle frontal gyrus	**52**	**34**	**34**	**48**	**0.001**	**5.33**

Table 1 MNI coordinates of significant clusters (p > 0.005, corrected for multiple comparisons, minimum cluster size = 25 voxels), number of voxels and p-value per cluster, as well as MNI coordinates and t-values of the maximally activated voxel in each cluster yielded by the parametric analysis of the magnitude of the total errors (external plus internal errors).

Correlation	Anatomical area	MNI			Cluster size (# voxel)	p-value	T score
		x	y	z			
Parametric analysis of external errors – positive correlation							
	Inferior frontal sulcus	**40**	**32**	**16**	**1562**	**<0.001**	**6.28**
	Inferior frontal gyrus	50	32	12			6.26
	Anterior insula	32	26	-6			5.08
	Middle frontal gyrus	**32**	**54**	**2**	**130**	**<0.001**	**3.62**
	Posterior medial	**6**	**24**	**58**	**117**	**<0.001**	**3.84**
	frontal cortex; BA 6/8	**6**	**36**	**58**			**3.20**
	Posterior medial frontal cortex; BA 8/9/32	**0**	**50**	**32**	**120**	**<0.001**	**3.93**
	Superior parietal lobe	**4**	**-72**	**56**	**78**	**0.003**	**3.07**
	Precuneus; BA 7	**-22**	**-56**	**46**	**56**	**0.031**	**3.63**
	Inferior frontal gyrus	**-48**	**30**	**30**	**334**	**<0.001**	**3.14**
	Basal Ganglia	**-18**	**-20**	**6**	**57**	**0.027**	**4.28**
	Cerebellum	**-18**	**-64**	**-38**	**52**	**0.027**	**4.87**

Table 2 Anatomical specification, MNI coordinates of significant clusters ($p > 0.005$, corrected for multiple comparisons, minimum cluster size = 25 voxels), number of voxels per cluster, p- and t-values of clusters yielded by the parametric analysis of the magnitude of the external errors.

Discussion

The aim of this study was to establish a relationship between neural activity and the magnitude of three types of errors: (1) motor errors committed by the agent (*internal errors*) (2) non-motor errors induced by environmental factors (*external errors*) and (3) the sum of these (*total errors*). For this purpose a sensorimotor transformation task was chosen in which participants committed motor errors of different magnitudes (*internal errors*) and in which incorrect feedback was given (*external errors*) during some trials.

We found that the activity of the MFG and the pMFC was enhanced with the magnitude of the *total error* as fed back to the subject, while the parametric analysis of the magnitude of *internal errors* alone revealed no significant correlation with activity in any brain region. Anterior insular and lateral prefrontal areas as well as cerebellar, parietal and pMFC (BA 6/8) activity were found to correlate positively with the magnitude of *external errors*.

The task used in this experiment differed from classical non-motor error paradigms (reviewed e.g. by Ridderinkhof et al., 2004). First, this task was not composed of a two or three-alternative forced-choice task in which the answer was either correct or incorrect and was therefore not limited to a dichotomous right or wrong feedback. This novel task extended beyond a qualitative analysis of the feedback to a quantitative analysis of error magnitude. Second, the required motor responses did not depend on a pure cognitive evaluation of a stimulus (e.g. stimulus A present or not), but on a transformation of visual input into a graded motor response.

5.4.3 Total error

One aim of this study was to determine the areas in which activity correlates positively with the magnitude of *total error* fed back to the subjects. The pMFC and the MFG/sulcus were positively correlated with *total error* magnitude. The source of this *total error* could either be of an *internal* nature only or a combination of *internal* and *external errors*. The confrontation with large error feedback is likely to induce several processes. Besides signaling an error, it may lead higher neural efforts for the correct planning, programming, execution as well as updating of the associated motor response.

The fact that we found activity modulation within the pMFC (BA 6/8) for errors is consistent with the results from error monitoring in cognitive tasks (e.g. Botvinick et al., 2001; Ullsperger & von Cramon, 2001; Ullsperger & von Cramon, 2001; Holroyd et al., 2004; Ullsperger et al., 2007; Li et al., 2008). When subjects are confronted with large errors, this may activate a process that calls for improvement of the motor response. Optimization of a motor response calls for new planning, which has been shown to trigger activity in the pre-SMA (Tanji, 1994; Picard & Strick, 2001). Furthermore, the pMFC has also been linked to signal the need to adjust behavior (Ullsperger et al., 2004) and it has also been shown that the intensity of pMFC activity allows predictions to be made about the strength of future adjustments (Kerns et al., 2004; Debener et al., 2005). Importantly, however, our behavioral findings reveal no such error adjustment. Thus, the interpretation that pMFC activity leads to future adjustments does not match our data. The activity we report here might instead reflect the signaling of a discrepancy between intended and actual outcome and thus the potential need to adjust performance. The lack of post-error adjustment might be due to the fact that our subjects had practiced the task ahead of scanning and were already stably performing at their optimum therefore no update would be implemented, which is different to previously described studies in the cognitive domain where learning was involved.

In addition to pMFC activity, bilateral MFG/sulcus activity was found to correlate positively with the magnitude of the feedback discrepancy. Since the medial and the dorsolateral prefrontal cortex are tightly linked anatomically (Luppino et al., 1993) and also a strong functional connectivity between these areas has been shown (Chaminade & Fonlupt, 2003) the dorsolateral prefrontal activity we find may be considered a pMFC co-activation. It has been suggested that the pMFC acts as a monitor, while the dorsolateral cortex as a controller (Ridderinkhof et al., 2004; Fletcher et al., 2001) or as a conflict solver (Casey et al., 2000), which interacts in the regulation of goal directed behavior. We might interpret the present activity of dorsal middle frontal cortex and anterior MFG in accordance to these studies as signaling the need to adjust behavior.

The total error corresponds to a mixture of *internal* and *external errors*. For a cognitive system it is important to be able to locate the source of error so that appropriate actions can be undertaken to prevent errors. For this reason in the following we separately investigate the specific contribution of the *internal* and *external errors* to these brain signals.

5.4.4 Internal errors

Another aspect of this study was to determine the areas where activity increases with the magnitude of the *internal motor errors*. Interestingly, we found no significant pMFC activity to correlate with the magnitude of *internal error*. This is somewhat surprising, since one would expect some analogies with the error monitoring previously investigated in the cognitive domain. These earlier studies consistently show pMFC activity to be triggered by error perception (e.g. Carter et al., 1998; Botvinick et al., 2001; van Veen et al., 2004; Ullsperger et al., 2007). One reason why no relation was found between error size and pMFC activity may be provided by the internal model theory (Kawato & Wolpert, 1998; Wolpert & Kawato, 1998). These internal models enable the agent to form a prediction about the sensory consequences of a motor action and to compare the predicted outcome with the actual outcome. At the same time research into error monitoring and perception in cognitive tasks has pointed out that pMFC is only activated when a deviation from an expected target is detected (Knutson & Cooper 2005; Bubic et al. 2009). Since the prediction of the sensory consequence of the motor command has already been made by the forward model, a deviation between target and feedback cue is not unexpected, and may therefore not trigger pMFC activity. Evidence for this line of argument may be seen in the fact that pMFC activity was only detected in trials in which *external errors* had been added in addition to the *internal errors* – a component that could not have been predicted by the forward model. Another hypothesis could be that correct feedback trials are the ones with the best possible outcome and that the need for adjustment could have been perceived as low. However, one should interpret these null-findings with caution. The absence of an effect may be due to experimental factors such as the sample size or any nonlinearities in the BOLD response that are not accounted for in the regression model.

5.4.5 External errors

The third aim of this study was to assess the activity of which brain areas positively correlate with the magnitude of the *externally* added error alone. To start with, we would like to comment on the fact that in trials including an *external error*, the size of explicitly fed back error is larger, on average, than in the remaining trials. However please note, it is the size of the *external error* component alone, rather than the (explicitly available) *total error*, which shows a significant correlation to activation size

in several additional brain regions. Thus, this *external error* component elicits significant reactions in the brain, which are discussed below.

Similar to the *total error*, the *external error* was also correlated with activity in the pMFC (BA 6/8), which conforms with results obtained from error monitoring in cognitive tasks (Botvinick et al. 2001; Ullsperger & von Cramon 2001; Fiehler et al., 2004; Holroyd et al., 2004; Ullsperger et al., 2007). In the incorrect feedback condition, feedback is distorted, and the outcome could not therefore be predicted correctly. We argue that the unexpected outcome triggered pMFC activity, which in return may have signaled the need to change behavior for outcome optimization. The same line of argumentation may also hold for the internal models, and we have indeed found cerebellar and parietal activity, as would have been predicted according to the work of several authors (Blakemore et al., 2001; Blakemore & Sirigu 2003; Imamizu et al., 2003; Imamizu et al., 2004; Imamizu & Kawato, 2009).

Besides regions of the error network we additionally found brain regions known to be involved in *affective* processes, such as anterior insula and lateral prefrontal cortex. Our analysis revealed IFG and anterior insular activity to increase with *external error* magnitude. The IFG is part of the lateral prefrontal cortex that supports the cognitive regulation of feelings and thoughts (Hariri et al., 2000; Kuchinke et al., 2005; Koelsch et al., 2006; Levesque et al., 2003; Ochsner et al., 2004; Baumgartner et al., 2006; Chiu et al., 2008). Furthermore it has been proposed that the insula, which is part of the ventral emotional system, is important for the identification of the emotional significance of the stimuli, the production of affective state responses and (as the IFG) involved in autonomic regulation of emotional responses (Lane et al., 1997; Buchel et al., 1999; Phelps et al., 2001; Phan et al., 2002; Phillips et al., 2003; Jabbi et al., 2008). Several studies dealing e.g. with negative emotions such omission of social reward (Siegrist et al., 2005), unfairness (Sanfey et al., 2003) or as frustration (Abler et al., 2005), report insular as well as IFG activity as observed in the current study. The magnitude of *external errors* in our study reflects the degree to which the individual performance has been distorted by external influences. This external feedback may be perceived as *unfair feedback*. E.g. in the study of Abler and colleagues (2005) participants were promised money when performing a task correctly, but the reward was omitted in some trials. In their study as well as in ours, subjects were presented with a worse outcome than would be expected from performance. They interpreted insular and IFG activation as being due to frustration and the need to regulate or inhibit pain distress and negative emotion.

In light of the abovementioned studies, a tentative explanation could be that adding *external errors* to the performance feedback results in emotional disturbance - the more so, the bigger the *external error* is. The question, however, arises whether such emotional consequences of distorted performance feedback depend on the subjects' conscious perception of a faulty feedback, or may be triggered by a feeling of uncertainty regarding performance outcome. Subjects were not always conscious of an external manipulation, but it is obvious from the statements gathered in the post experiment questionnaire that being confronted with error induced negative emotions in the subjects. Answers to the question “what was your reaction to an error?” ranged from “I tell myself to do better in the next trial”, “the device must be out of whack”, “frowning”, “being annoyed”, “upset”, “irritated” to “frustrated”. This is comparable to a tennis player who gets emotionally agitated after missing a ball and might either attribute the failure to environmental causes or to his skills. From our verbal reports alone, it is difficult to specify the attributional style, or locus of error, subjects have assumed in each trial. We abstained from asking subjects about their reactions after every trial, since that would undoubtedly have introduced bias in the subject’s manner of dealing with errors, and the focus of this study was to investigate whether the brain reacts differently to errors from different sources. Thus, in our study subjects might have occasionally felt that they were unable to influence the result and to adjust their behavior in order to avoid these errors. However, this will have only been true for a small subset of trials because external errors ranged from very small and unnoticeable to very large and clearly noticeable.

In a task in which the manipulation is mastered, unpredictable events, which are included infrequently, such as *external errors* may be perceived as deviants. Taking this into account, we would like to shortly discuss common aspects of oddball paradigms and the present experiment. At unpredictable times subjects are confronted with unexpected stimuli which in oddball settings has been shown to consistently activate a large network including parietal, medial and lateral frontal areas (Kiehl & Liddle, 2001; Huettel & McCarthy, 2004). Being confronted with unexpected stimulation may have induced an attentional modulation in our experiment comparable with oddball experiments. This activity pattern classical to oddball paradigms is largely consistent with ours. However our task differs in several aspects from oddball paradigms. First the successful manipulation relies on an active sensorimotor integration of visual stimuli into a motor response, which induced a sense of agency not common to oddball paradimgs. Second the output has to be monitored and in case of a mismatch between expected and actual outcome, in order

to optimize behavior, the source of such a mismatch has to be located. Additionally, in the present study, reactions to unexpected stimuli evoke emotional responses going beyond classical oddball tasks. Therefore, despite common aspects, our task interpretation cannot be equaled to one of oddball paradigms.

In summary, we can postulate that anterior insular and IFG activity reflects the emotion induced by the *external errors*, that the pMFC results from exposure to an unexpected event and, finally, that cerebellar-parietal activity may reflect adjustments of the internal model. To explicitly address the issue of awareness of the source of error, a future study is planned.

5.4.6 Conclusion

Our experiment yields three major conclusions: 1) pMFC (BA 6/8) and bilateral MFG activity correlates positively with the magnitude of *total errors*. The larger the errors with which subjects were confronted, the higher the perceived need to adjust behavior or an internal model relating action to expected outcome. 2) Activity in pMFC (BA 6/8), anterior insula, cerebellum, precuneus and IFG correlates with the magnitude of *external errors*. Presumably, these regions reflect a negative emotional response evoked while facing unexpected and potentially unfair feedback. 3) pMFC activity does not significantly correlate with the size of *internal errors*. The fact that pMFC correlates with *external errors* and with *total errors* but not with *internal errors* leads us to assume that *internal motor errors* are processed differently from non-motor errors. One explanation for this may be given by the framework of internal models. These internal models enable the sensory consequences of motor commands to be predicted, and these errors are therefore not unexpected. Detection of motor and non-motor error apparently relies on different neural networks.

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6. Study 3

Performance Feedback and Monetary Reward Processing in the Dorsal and Ventral Striatum

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6.1 Abstract

When an agent receives reward, activity in its striatum is increased. Such activity is not only observed during monetary reward, but also when the agent receives positive feedback about successful performance. In the former case striatal activity reflects *extrinsic* reward processing, while in the latter, striatal activity potentially reflects the *intrinsically* rewarding effects of performing well. There are interactions between extrinsic and intrinsic reward. Most importantly, there can be a "hidden cost of reward", which is a potentially detrimental effect of extrinsic (e.g. monetary) reward on intrinsic reward. If people learn to perform for money then they might not be motivated so well any more to work for positive feedback alone. This raises the question if a positive feedback, among trials in which high performance is linked to monetary reward, still elicits striatal activity. To address this, we used a monetary incentive delay task. In all trials participants received positive and negative feedback depending on their performance. In half of the positive feedback they could additionally receive monetary reward if they performed well. This resulted in high performance trials, which were monetarily rewarded and high performance trials that were not. This allowed us to dissociate the neural correlates of performance feedback alone from the neural correlates of monetary reward that is linked to high performance. Our data suggest that the *ventral striatum* is primarily sensitive to feedback about high performance. The *dorsal striatum* on the other hand is only activated by monetary reward.

6.2 Introduction

Reward is generally defined as a stimulus an organism is willing to work for (Knutson & Cooper, 2005). Reward is further divided into primary (e.g. food, juice, sex) and secondary (e.g. money) reward. The striatum is a key neural locus of reward

processing. It is classically divided into a ventral and dorsal part (Knutson et al., 2008). The dorsal striatum consists of the dorsal part of the putamen and caudate while the ventral striatum consists of the nucleus accumbens (NAcc) and the ventral part of the caudate and putamen (Mawlawi et al., 2001).

It has been proposed that the ventral striatum encodes reward *anticipation* while the dorsal striatum codes reward *reception* (Knutson et al., 2001; Knutson et al., 2001; Knutson & Cooper, 2005). However, there also findings which are hard to reconcile with this view. Primate studies report activity in the dorsal striatum both during receipt and anticipation of reward (Hollerman et al., 1998; Schultz et al., 2000). Human functional imaging studies also show inconsistent results. For example, activation of the ventral striatum has been found for anticipation of money (Knutson et al., 2000; Breiter et al., 2001; Roesch & Olson, 2007) as well as for reward outcome (Delgado et al., 2000; Breiter et al., 2001; Delgado et al., 2003; Delgado et al., 2004). Additionally, the dorsal striatum is not only activated by classical primary and secondary reward, but also by feedback about positive performance (Shidara et al., 1998; Tricomi et al., 2004; Tricomi et al., 2006). The ventral striatum is also activated by the presentation of stimuli with positive valence (Aron et al., 2004; Sabatinelli et al., 2007; Kirk et al., 2009). Taken together, the differential roles of ventral and dorsal striatum have not been finally resolved.

Reward processing has also been examined in cognitive psychology, where an important focus lies on the comparison between extrinsic and intrinsic reward and their mutual influence on each other (Reitman, 1998; Deci et al., 1999; Frey & Jegen, 2001; Deci et al., 2001). Extrinsic reward refers to the receipt of e.g. food or money for a specific activity. Intrinsic reward refers to someone receiving no apparent external incentive for a certain behavior, but instead the activity itself seems to be rewarding (Deci, 1971).

In the present study we have used functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms of these two types of reward. We operationally define *extrinsic reward* as the receipt of money for a high accuracy of performance, while we define *intrinsic reward* as positive feedback about such high performance in accordance with theories of motivation for achievement and competence (Deci 1971).

Importantly, we also aimed to investigate any potential interactions between the two forms of reward. Extrinsic reward enhances performance and productivity, but there might also be “hidden cost of [extrinsic] reward”. Many experiments have suggested that extrinsic reward can, under certain circumstances, *undermine intrinsic reward mechanisms* and thus lead to a decrease in productivity or performance (Kohn, 1993;

Deci et al., 1999; Callan & Schweighofer 2008). Here we investigate the possible negative influence of extrinsic reward on intrinsic reward in order to see if positive feedback about performance still elicits striatal activity even when extrinsic reward is missing.

6.3 Methods

6.3.1 Participants

Nineteen healthy volunteers participated in this study (mean 27.8 years, SD: 3.8, 6 males). Prior to scanning, all subjects were tested for handedness ensuring they were classified as right handed (Annett, 1970). Subjects performed two scanning runs, which were separated by a short break (1-2 min). Task and testing procedures were in accordance with the institutional guidelines of the Declaration of Helsinki and the study was approved by the local ethics committee. The subjects were naïve to the purpose of the experiment and received 15 CHF for their participation (approx. 15 US-Dollars) plus the money they earned during the experiment. All gave written informed consent.

6.3.2 Task Design

To examine the influence of reward and performance on brain activity, a modified monetary incentive delay task (MID) was chosen (Knutson et al., 2000) where the task was to apply a force to a force grip device that was defined by a cue on a trial-by-trial basis.

On every trial subjects were first presented with one of two possible reward indicator cues (1.5 ms, see Fig. 1). A cue showing gold bars announced that money could be earned on this trial, the amount of which depended on performance (monetary reward option trial, MRO). A cue with crossed out gold bars indicated that regardless of subjects' motor performance, no money could be earned (no monetary reward option trial, NMRO). After a random delay period of 3 to 7 s showing a fixation cross, a yellow target cue was presented for 4.5 to 8.5 s. The target cue consisted of a square positioned at a random position along a horizontal line. The target's position along the line indicated the required motor response. As soon as the target cue appeared on the screen, subjects were to manipulate the force-grip device and were subsequently given feedback for 3 to 7 s about their performance in form of a red

square below the line. The distance between target and feedback cue was used to indicate the error. Additionally, in trials with reward option, subjects were informed about the amount of money they had earned in the present trial and how much they had earned up to then during the whole experiment. This information was given at the same time as the performance feedback. In trials without reward option, a double X was presented instead of the trial specific gain to keep the visual input similar. Directly after offset of the feedback screen, subjects were asked to release pressure on the force-grip device and a new trial started. Each trial lasted between 12 and 24 seconds, depending on the trial-specific jitter (Fig. 1). The whole experiment lasted 48 min on average.

6.3.3 Apparatus

For recording of motor responses we used an MRI-compatible isometric force-grip device (isometric force-grip device, Sensory-Motor Systems Laboratory, ETH Zurich and University of Zurich), which was set to measure isometric grip force from 0 to 40 N in 8 bit resolution with a sampling frequency of 60 Hz. The applied force was transformed into a feedback cue positioned along a horizontal line. Minimal and maximal forces were introduced to prevent the feedback cue being outside a specific range. Forces less than 10 N were always coded by the leftmost position, whereas the forces larger than 40 N were translated into the rightmost position on the line. Such a low force range was chosen to minimize muscle fatigue and to avoid possible confounds in the brain activation data by force coding. Between 10 to 40 N forces were linearly transformed into an according position on the line.

The horizontal line had a width of 620 pixels. The error range in which money could be earned was between 0 to 160 pixels deviation. The amount of money earned was calculated as follows: amount of money in cents $R = 100 – m(5/8)$ for $m < 160$ pixels, and $R = 0$ for $m \geq 160$ pixels, with m describing the number of pixels between target and feedback cue. Zero pixel deviation resulted in a gain of 1 CHF while errors equal or bigger than 160 pixels resulted in no gain. The gain of money was negatively correlated with the motor error, which resulted in a linear increase of gain with performance. The two trial types (MRO/NMRO) and the division of the performance into sufficient (error < 160) and insufficient (error > 160) to gain money lead to four possible outcomes (table 1; Fig. 2), which are the basis for further analysis.

6.3.4 Experimental setup

Prior to scanning, subjects were informed about the study and any fMRI contraindications were checked. Before starting with the functional measurements, a short training session including 50 trials was performed by the participants to make sure they had understood the task. This further allowed familiarizing them with the task and with handling of the force-grip device and to stabilize performance. During both scanning sessions, participants lay supine in the scanner. Head movement was minimized using an adjustable vacuum cushion. Visual stimuli were projected onto a translucent screen that subjects viewed from inside the scanner via a mirror above their head. The force-grip device was placed in their right hand. Stimulus presentation and response collection were controlled by “Presentation 11.2” software (Neurobehavioral Systems, Inc, Albany, USA). Routinely, individual T1-weighted anatomic brain images were recorded before the actual experiment sessions started. After the experiment, subjects were asked to complete a questionnaire confirming correct task performance and reporting their experiences during scanning.

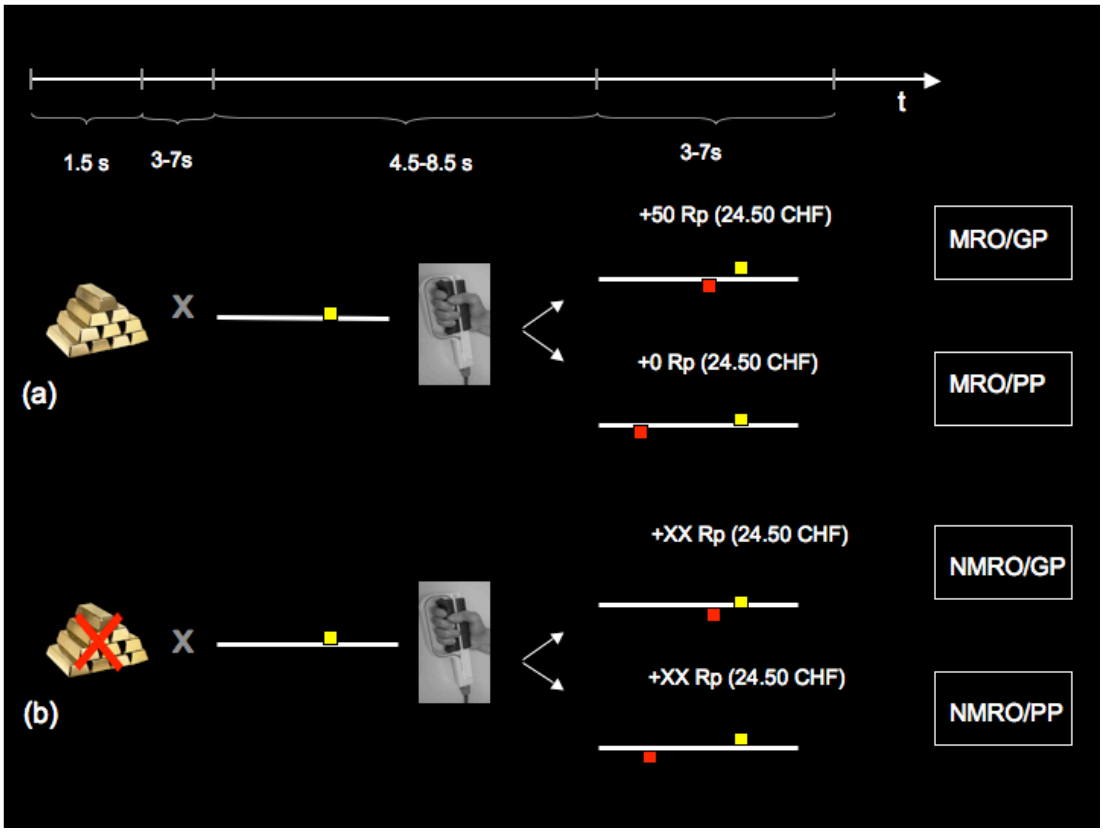

Fig. 1 In each trial, subjects were first presented with the instruction cue, which defined the nature of the next trial. There were two types of trials, potential reward trials (MRO) and no monetary reward trials (NMRO). In the former subjects could earn money depending on their motor performance (a) and in the latter no money could be earned regardless of subject’s performance (b). After trial specification, a

yellow target square was presented above the line. Then subjects had to manipulate the force-grip device in order to evoke a force matching to the target's position on the line. After a variable interval (3-7 seconds) they were given visual feedback about their performance in form of a red square appearing at the location below the line matching their applied force. The distance between the target and feedback was considered the motor error; the closer these two, the better the subjects' motor performance. Additionally in MRO they were informed about the amount of money they just had earned and the cumulative total at that point. After the presentation of the feedback, a new trial began. For analysis purpose feedback was divided into two categories (good/poor). Good performance equals outcomes that led to monetary gain, while poor performance didn't.

6.3.5 Analysis of behavioral performance

We calculated the average magnitude of motor errors separately for the MRO- and the NMRO- trials and compared the means using a paired t-test. We also investigated whether subjects improved their motor performance during the course of the experiment. To this end, we calculated two regression analyses of the averaged motor performance over time and compared these two outcomes. In addition, the amount of money that had been earned and the number of trials for each outcome possibility (trial type x performance level) was assessed.

6.3.6 Functional imaging

Functional magnetic resonance imaging was performed at the University Hospital of Zurich on a Philips Achieva 3-T whole-body MRI system (Philips Medical Systems, Best, The Netherlands), equipped with a Philips eight channel SENSE head coil. Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted three-dimensional spoiled gradient echo pulse sequence (180 slices, TR = 20 msec, TE = 2.3 msec, flip angle = 20°, FOV = 220 mm × 220 mm × 135 mm, matrix size = 224 × 187, voxel size = 0.98 mm × 1.18 mm × 0.75 mm, resliced to 0.86 mm x 0.86 mm x 0.75 mm). Functional data were obtained in 606 scans per run consisting of 33 slices covering the whole brain in oblique acquisition orientation. The acquisition of the slices was in ascending acquisition order (slice thickness 4 mm and inter-slice-gap of 2 mm), using a sensitivity encoded (SENSE, factor 2.0), single-shot echo planar imaging technique (TR = 2.5 sec; echo time, TE = 35 ms; FOV= 220 mm × 220 mm × 132 mm; flip angle = 78°; matrix size = 80 × 80; voxel size = 2.75 mm × 2.75 mm × 4 mm, resliced to 1.72 mm × 1.72 mm × 4.00 mm). Three dummy scans at the beginning of each run were acquired and discarded in

order to establish a steady state in T1 relaxation for all functional scans to be analyzed.

6.3.7 Data analysis

Artifact minimization and MRI data analysis were performed using MATLAB 2006b (Mathworks Inc., Natick, Massachusetts, USA), and the SPM5 software package (Institute of Neurology, London, UK http://fil.ion.ucl.ac.uk/spm).

All images were realigned to the first volume, normalized into standard stereotactical space (using the EPI-template provided by the Montreal Neurological Institute, MNI brain), resliced to 2 mm × 2 mm × 2 mm voxel size and smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel. After highpass-filtering (cut-off 128 sec), an individual statistical general linear model (GLM) was computed for each participant (Friston et al., 1995). The GLM model contained twelve regressors: six for the MRO-trials and six regressors for NMRO-trials. Both trials type were modeled in the same way. For illustration, the regressors for the MRO trials are described in detail.

Regressors for "MRO-trials": The first regressor for reward option trials was the presentation of the cue (goldbars) that indicated to subjects whether they could obtain reward or not. This was modeled as an epoch lasting 1.5 sec. A second regressor was the target presentation, which was modeled as an epoch starting from target cue onset and lasting until the onset of the feedback. Thus, the duration of this epoch was variable from trial to trial. The third regressor was a 1 sec epoch starting at the onset of MRO feedback presentation, modeling the trials with error magnitude smaller than 160 pixels deviation. This corresponds to the trials that were monetarily rewarded. The fourth regressor was modeled as an epoch lasting 1 sec for the feedback of MRO trials with error magnitude >160 (poor performance (PP)), which resulted in no monetary reward. The four regressors for the NMRO trials were modeled accordingly.

For population-level inferences, maps of contrast coefficients for each individual contrast were collectively submitted to one-sample t-tests against the null hypothesis of no activation in a random effects analysis. In order to determine average activation for the four outcome conditions, two trial types (MRO/NMRO) x performance level (PP/GP); were subjected to a second-level analysis at the time point of *outcome presentation*.

Considering that the main goal of this study was to investigate the neural impact of performance and reward on the striatum, these brain regions were subjected to ROI-

analyses. Functionally, the NAcc and the ventral part of the caudate and putamen are counted to the ventral striatum, while the dorsal part of the caudate and the putamen belong to the dorsal striatum (Knutson et al. 2008). To investigate these substructures, ROIs from the caudate, putamen and NACC as provided by Harvard/Oxford cortical and subcortical structural atlases (www.cma.mgh.harvard.edu) were further subdivided to fit the dorsal respectively the ventral striatum. To do so, the caudate ROI was split at an axial plane through the anterior commissure (Mawlawi et al., 2001), the dorsal part of the head, body and tail were labeled dorsal caudate, while the part ventral of the anterior commissure was labeled ventral caudate. A similar procedure was applied to the putamen: it was cut at the axial plane through the anterior commissure and slices dorsal to it were labeled dorsal putamen, slices ventral the anterior commissure were labeled ventral putamen (Mawlawi et al., 2001).

To reveal how feedback processing is influenced by the quality of performance and monetary reward, an in-house Matlab ROI-analysis routine was used. In this ROI-analysis, contrast values (i.e. beta values weighted according to the contrast vectors described above) were averaged within each of these regions for the contrasts "Feedback". This resulted in an average effect size for each region and contrast per subject. These were analyzed by a two-way repeated-measures ANOVA with performance (good vs. poor) and trail type (MRO vs. NMRO) as within-subject factors and Bonferroni-corrected for multiple comparisons. To determine whether the ventral and dorsal striatum activity significantly differed from the against baseline null hypotheses, these two structures were subjected to one-paired t-tests (Table 1).

6.4 Results

6.4.1 Behavioral Results

Subjects were only included in the analysis when they fulfilled a minimum of 10 trials in each outcome condition (MRO/GP; MRO/PP; NMRO/GP; NMRO/PP). Therefore, 4 subjects had to be excluded from the analysis, which resulted in a final sample of 15 subjects. On average, 44.60 CHF were earned per subject, with a SD of 10.80, minimum of 30.00 CHF and maximum of 56.00 CHF. The mean error magnitude was 143.3 ± 29.9 in MRO-trials and 157.7 ± 33.2 in NMRO-trials. Subjecting these two means to a paired t-test yields no significant difference (t= -1.348, df= 14, p=0.199).

To investigate whether performance changed over time, a regression between trial number and performance was calculated. The regression analysis, using the enter method, revealed no significant change in performance for the NMRO- trials ($F_{1,78}$

=0.508, p = 0.478, adjusted R^2 = -0.006), neither for the MRO-trials ($F_{1,78}$ =2.935, p = 0.09, adjusted R^2 = 0.024), although a trend towards improved performance could be suggested here.

6.4.2 Functional MRI

The main focus of our study was placed on brain regions of the ventral and dorsal striatum and their activity level induced by performance feedback and reward. Therefore, the mean activity levels within these regions (Table 3) for the four outcome conditions were calculated, subjected to a repeated measures ANOVA (Table 4) and, to determine which pairs of conditions significantly differ, mean values were compared with post hoc paired t-tests (Table 5).

Ventral striatum: The results of the repeated measure ANOVA revealed a significant main effect of intrinsic reward (good performance) in the ventral striatum substructures, but none of extrinsic reward. The interaction effect of reward and performance although was significant in all the three substructures of the ventral. Paired t-tests revealed significant differences (corrected for multiple comparisons 0.05/n-t-test) for the all the ventral striatum subcomponents between the conditions MRO/GP und MRO/PP, but no significant differences between MRO/GP und NMRO/GP (Fig. 2). In other words, the activity level induced by good performance does not significantly differ for rewarded and not rewarded trials (MRO/GP vs. NMRO/GP), while the activity level related to performance level (poor/good) does (MRO/GP vs. MRO/PP).

Dorsal striatum: The ANOVA for the dorsal striatum substructure revealed no significant main- or interaction effects in the dorsal putamen (Fig. 3). However, in the dorsal caudate a significant main effect of reward option was detected. This reward option effect describes the possibility of getting monetary reward, not telling anything about if reward that has been earned or not. The simple option of possibly making money increases activity. However, significant effect of performance and of interaction failed to be significant. Paired t-tests for the comparisons MRO/GP vs. MRO/PP and MRO/GP vs. NMRO/GP in the dorsal caudate both reveal significant differences. The activity level for the rewarded trials was significantly higher than for all other conditions. This holds true for uncorrected t-tests. However, despite of insignificant results for corrected data, there is a strong trend that dorsal striatal activity is mainly induced by monetary reward at not by performance feedback.

Trial Type	Performance Feedback	Monetary Reward	Abbreviation
Monetary Reward Option (MRO)	Good Performance (GP)	Monetary Reward	MRO/GP
Monetary Reward Option (MRO)	Poor Performance (PP)	No Monetary Reward	MRO/PP
No Monetary Reward Option (NMRO)	Good Performance (GP)	No Monetary Reward	NMRO/GP
No Monetary Reward Option (NMRO)	Poor Performance (PP)	No Monetary Reward	NMRO/PP

Table 1. List of experimental conditions and abbreviations

Anatomical area	Condition	T value	df	p-value one-tailed (Bonferroni corr.)
Dorsal striatum				
	MRO/GP	6.175	14	<0.001
	MRO/PP	4.429	14	<0.001
	NMRO/GP	4.834	14	<0.001
	NMRO/PP	4.159	14	<0.001
Ventral striatum				
	MRO/GP	6.401	14	<0.001
	MRO/PP	3.602	14	<0.001
	NMRO/GP	5.816	14	<0.001
	NMRO/PP	4.300	14	<0.001

Table 2. One-paired t-tests testing ventral and dorsal striatum ROI activity against null hypothesis. Both structures reveal to be significantly different from the null hypothesis in the four outcome conditions.

Anatomical area	Condition	Mean	SD	Nb. of trials mean	Nb. of trials SD
Dorsal caudate					
	MRO/GP	3.03	3.20	49.1	16.5
	MRO/PP	1.92	3.41	32.5	17.2
	NMRO/GP	1.46	2.83	46.3	14.5
	NMRO/PP	1.27	2.89	31.1	13.7
Dorsal putamen					
	MRO/GP	6.30	3.27	49.1	16.5
	MRO/PP	5.61	3.98	32.5	17.2
	NMRO/GP	5.38	3.25	46.3	14.5
	NMRO/PP	5.21	3.88	31.1	13.7
Ventral caudate					
	MRO/GP	3.61	2.83	49.1	16.5
	MRO/PP	1.61	3.34	32.5	17.2
	NMRO/GP	2.39	2.92	46.3	14.5
	NMRO/PP	1.81	2.89	31.1	13.7
Ventral Putamen					
	MRO/GP	6.82	3.66	49.1	16.5
	MRO/PP	5.05	3.43	32.5	17.2
	NMRO/GP	5.73	2.69	46.3	14.5
	NMRO/PP	5.25	3.36	31.1	13.7
Nc Accumbens					
	MRO/GP	4.30	3.03	49.1	16.5
	MRO/PP	1.50	3.33	32.5	17.2
	NMRO/GP	3.03	2.34	46.3	14.5
	NMRO/PP	2.10	2.56	31.1	13.7

Table 3. Mean and SD of beta-values for dorsal and ventral striatum-ROI listed separately for all four outcome conditions.

Anatomical area	Main effect reward option	Main effect performance	Interaction
Dorsal Caudate	F(1,14)= 17,7, p = 0.001**	F(1,14)= 3,435, p =0.085	F(1,14)= 4,42, p = 0.054
Dorsal Putamen	F(1,14)= 0.800, p =0.386	F(1,14)= 2.964, p = 0.107	F(1,14)= 1,718, p = 0.211
Ventral caudatus	F(1,14)= 0.505, p =0.489	F(1,14)= 43.919, p < 0.001**	F(1,14)= 7.325, p = 0.017*
Ventral putamen	F(1,14)= 0.313, p =0.584	F(1,14)= 22.071, p < 0.001**	F(1,14)= 6,164, p = 0.026*
NAcc	F(1,14)= 0.263, p =0.616	F(1,14)= 95.863, p < 0.001**	F(1,14)= 16,05, p = 0.001**

Table 4. Effects of main and interaction for the dorsal and ventral striatum ROI. For the dorsal caudate a significant main effect for reward option was revealed but none for the performance. The interaction missed significance level by little. On the other hand, the ventral structures show a different pattern. There a significant performance main effect was detected as well as a significant interaction.

Dorsal Caudate		MRO/ PP	NMRO/ GP	NMRO/ PP	Nucleus Accumbens		MRO/ PP	NMRO/ GP	NMRO/ PP
	MRO/ GP	**0.004** 3.44	**0.029** 2.42	**0.018** 2.68		MRO/ GP	**<0.001** 9.155	0.100 1.764	**0.003** 3.590
	MRO/ PP		0.438 0.799	0.316 1.039		MRO/ PP		0.059 -2.054	0.380 -0.906
	NMRO /GP			0.354 0.959		NMRO/ GP			**0.008** 3.105
Vental caudate		**MRO/ PP**	**NMRO/ GP**	**NMRO/ PP**	**Ventral putamen**		**MRO/ PP**	**NMRO/ GP**	**NMRO/ PP**
	MRO/ GP	**<0.001** 5.92	0.143 1.592	**0.018** 2.684		MRO/ GP	**0.001** 4.367	0.207 1.324	0.099 1.768
	MRO/ PP		0.353 -0.961	0.800 -0.257		MRO/ PP		0.378 -0.911	0.813 -0.241
	NMRO /GP			0.085 1.850		NMRO/ GP			0.199 1.663

Table 5. List of all the performed T-tests. For each anatomical structure all the outcome conditions were compared with each other. T-values are corrected for multiple comparisons. The dorsal caudate displays a significance pattern revealing the MRO/GP condition to be larger in activity than all the three other outcome conditions.
The ventral structures show a different pattern: a significant difference is found for the MRO/GP and MRO/PP as well as for the MRO/GP and NMRO/PP and the NMRO/GP and NMRO/PP.

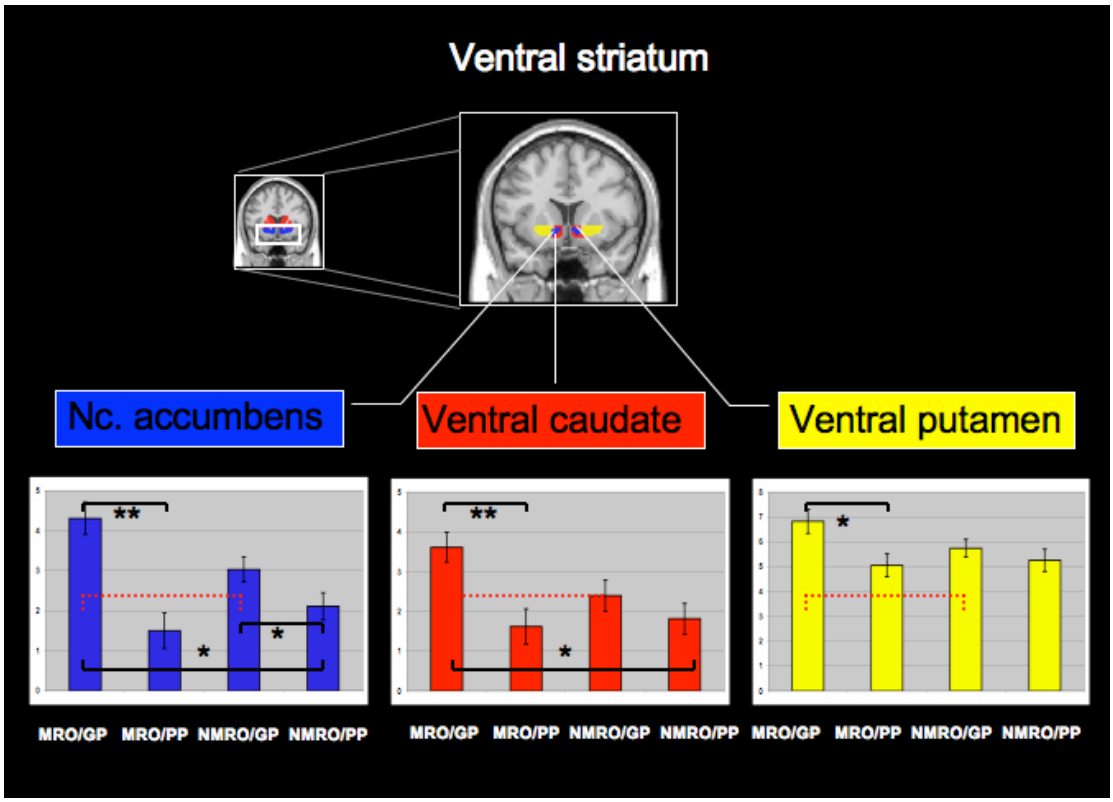

Fig. 2 The figure depicts the results of the ROI-analysis for the ventral striatum. The activity level for each outcome condition is mapped for the substructures of the striatum. The y-axis describes the effect size expressed as mean beta values. (** tags significant results corrected for multiple comparisons, * describes significant results uncorrected for multiple comparisons.)
ANOVA for repeated measures revealed a significant main effect for performance and a significant interaction effect for performance and monetary reward. Paired t-tests revealed for each substructure a significant activation level between poorly and well performed trials in the MRO condition, but no significant differences for the well solved trials, regardless of the potential monetary reward. This suggests that the ventral activity, especially the NACC is sensitive to both, good performance and monetary reward. Good performance alone increases NACC activity but clearly it's activity is also driven by monetary reward.

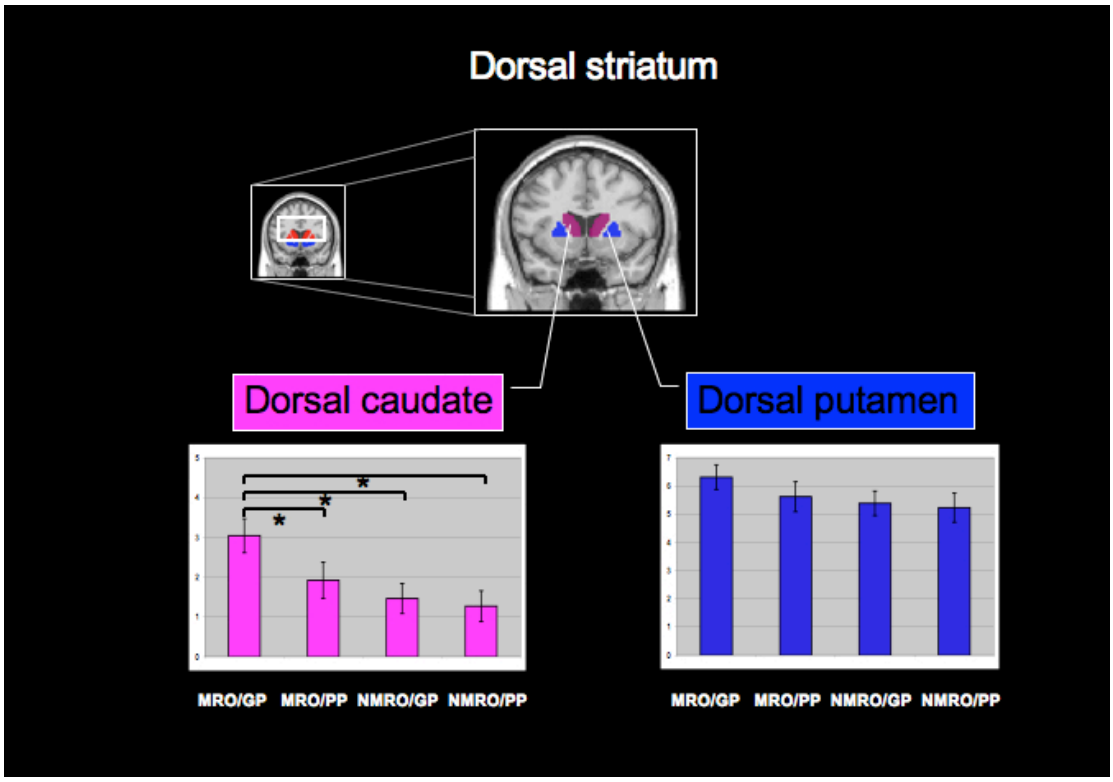

Fig. 3 The figure depicts the results of the ROI-analysis for dorsal striatum. The activity level for each outcome condition is mapped for the substructures of the striatum. The y-axis describes the effect size expressed as mean beta values. (** tags significant results corrected for multiple comparisons, * describes significant results uncorrected for multiple comparisons.)
ANOVA for repeated measures revealed a significant main effect for performance and no significant interaction effect for performance and monetary reward. Paired t-tests revealed dorsal caudate activity to be significantly higher for monetarily rewarded trials and significantly lower in the other conditions. This clearly indicates that dorsal caudate activity is elicited by monetary reward and not by positive feedback. On the other hand, dorsal putamen activity is neither driven by by performance, nor by monetary reward.

6.5 Discussion

The present study used fMRI to investigate the modulation of human striatal activity by performance feedback with and without monetary consequences. For this purpose a modified monetary incentive task was chosen, in which subjects' high performance was monetarily rewarded only on half of the trials. Our results differentiate ventral and dorsal striatum according to their relative contributions to coding high performance and monetary reward. Results show that ventral striatum activity is driven by high performance feedback, which could be considered a form of intrinsic reward (good performance/achievement). On the other hand, there is strong evidence that the dorsal striatum activity is driven by (extrinsic) monetary reward.

6.5.1 Behavioral results

Analysis of behavioral results showed that the average error rate did not differ between the two conditions. Regression analyses revealed a trend towards improvement over time for the MRO-trials, but not for the NMRO-trials. The fact that MRO-trials were not performed significantly better than NMRO-trials and that these two types of trials did not clearly improve questions the intuitively appealing assumption of beneficial influences of monetary reward on performance in our task setting. Please note that our task differs from a probabilistic reward task in that subjects are informed *before each trial* as to whether they can obtain a reward by achieving a high performance. From an economic point of view one would expect reward to enhance the performance level, since subjects are likely to be more motivated and/or attentive when they can obtain money for their performance. On the other hand, many psychological experiments have suggested that under certain conditions reward may undermine intrinsic motivation and crowd out the positive and pleasant effect of a well solved task (for review see Deci et al., 1999; Frey & Jegen, 2001). Some behavioral studies have demonstrated a positive relationship between monetary reward and cognitive performance, e.g. in word retrieval tasks (Nielson & Bryant, 2005; Adcock et al., 2006) and other studies post the opposite (Spence, 1970; Callan & Schweighofer, 2008). In our study, potential monetary reward neither significantly enhanced nor deteriorated performance and absence of monetary reward did not significantly dampen performance in the NMRO-trials. Since it was not possible to directly control for motivation and emotion during the experiment, several possible contributions of these psychological states will be briefly discussed in the following.

The question arises whether motivation was equal during rewarded and unrewarded trials and whether potential differences in motivation favored learning. Taking into account that the task was the same in both conditions and conditions were randomly swapped, we can exclude that subjects learned the task better in one condition than in the other. However, the trend in improvement over time in monetarily rewarded trials indicates, that subjects may have spent more effort and were possibly more motivated during the MRO-trials. It is also conceivable that subjects may have considered the NMRO-trials as exercise trials in which they could improve their motor ability and later apply it in the MRO-trials. Thus they could have remained equally motivated and attentive throughout the different conditions. Another question concerns the rewarding quality of positive feedback. It is quite likely that subjects

may have considered it rewarding to perform well per se, regardless of monetary consequences.

6.5.2 Ventral striatum

A surprising and intriguing result from this study is that trials that were not extrinsically rewarded, elicited activation in the ventral striatum comparable to monetarily rewarded trials as long the performance level did not differ (MRO/GP vs. NMRO/GP). In contrast, significant differences in activity level were found between high and low performed trials in monetarily rewarded trials (MRO/GP vs. MRO/PP), and such a trend was even found in the condition in which no monetary reward was to be expected at all (NMRO/GP vs. NMRO/PP). Such an activity pattern was found for the NAcc, and the ventral caudate which indicates that, concerning the process under investigation, the NAcc and the dorsal caudate work as a functional unit and it is justified to consider the "ventral striatum" as a joint structure. Even though the ventral part of the putamen is counted to the ventral striatum (Mawlawi et al., 2001), considering its deviant activity pattern, it arises the question whether it should be counted to the ventral striatum.

Taken together, in the current setting, extrinsic reward does not impair ventral striatum activity to positive outcome when not linked to monetary reward. However, a significant interaction between extrinsic reward and performance was observed. This indicated that ventral striatum activity is mainly driven by performance feedback but also is also sensitive to the possibility of getting extrinsic reward. In functional reward research, the ventral striatum has classically been implicated in processing of reward and reward anticipation (Knutson et al., 2001; Knutson et al., 2001; Cooper et al., 2009). In the past few years however, a growing number of studies have suggested that the role of the ventral striatum should be viewed more generally in terms of processing of informationally salient events rather than specifically in terms of extrinsic reward (Horvitz, 2000; Zink et al., 2003; Phan et al., 2004). For example, Aron and colleagues (2004) found that even "purely cognitive feedback" indicating a positive outcome engaged NAcc activity. In our study subjects received only cognitive feedback, which activated ventral striatum in the NMRO condition.

Further studies have extended the implication of the ventral striatum in processing positive feedback to processing pleasant stimuli. In a study by Sabatinelli and colleagues (2007) subjects were shown pleasant images of erotic and romantic couples and equally salient, but neutral pictures. Their results revealed that NAcc is sensitive to the pleasantness of events. Similar results have been found in a study in

which subjects had to rate the pleasantness of pictures (Kirk et al., 2009) or the attractiveness of faces (Aharon et al., 2001). Obviously, rating and watching pleasant pictures may not be comparable to performing well in a sensorimotor transformation task, but there are common core characteristics, most importantly facing a good and pleasant outcome without getting any apparent physical reward for it.

On the other hand the NAcc has also been linked to the aversive stimuli (Becerra et al., 2001), such as physical and psychological pain, (O'Connor et al., 2008) stressing events as well as to anticipation of aversive events (Levita et al., 2009). E.g. Wiswede and colleagues (2009) have shown that emotion can modulate error and possibly also reward processing. The situation, in which subjects performed well but were not rewarded, may be frustrating, disappointing or generally considered as an unpleasant event. Since no data about subjects' thoughts are available, this interpretation cannot be completely ruled out. However, this interpretation is mitigated by the assumption that negative emotions could not only be elicited by omission of rewards, but also by repeated failure in the same task. Consequently, negative emotion could be the greatest or at least equally strong in the condition in which subjects could have won money but performed poorly. If negative emotion was the driving force for NAcc activity, it would be very likely to find highest NAcc activity in the condition in which subjects could have won something if they had been performing well but failed. An alternative interpretation for NAcc activity has been proposed by Zink and colleagues (Zink et al., 2003; Zink et al., 2004). They claim that NAcc is innervated by presentation of salient stimuli and define saliency as frequency of a stimulus presentation. Our data clearly speak against this view, since we find the highest NAcc activity for the trial type that occurred most.

To summarize, we assume that the ventral striatum activity is primarily influenced by positive performance feedback (and not by saliency) and that the rewarding qualities of this positive feedback may be interpreted in line with studies showing NAcc activity due to a pleasant outcome. Even though we did not explicitly record subjects' emotion during the experiment, it is possible that a successful performance and the pleasure derived from a positive outcome may be sufficient to induce a rewarding experience. However, a significant interaction between performance level and monetary reward option was found, indicating that ventral striatum activity is also driven by the option of possibly getting money. The ventral striatum seems to represent the total reward value and that both, positive feedback and option of possibly making money increase the total reward value. A very interesting and new finding is that trials, which are rewarded by positive performance feedback, elicit

ventral striatum activation comparable to trials, which additionally give monetary reward.

6.5.3 Dorsal striatum

To shed light on the ambiguous implication of the ventral and dorsal striatum in reward processing, we also analyzed the dorsal striatum with respect to its sensitivity to performance and monetary reward. The dorsal striatum reveals a different pattern of activation than the ventral striatum. A detailed analysis of the subcomponents (dorsal putamen and dorsal caudate) of the dorsal striatum revealed that the two differ in their response to reward and feedback. While activity in the dorsal putamen does not significantly differ between the different outcomes at all, the dorsal caudate shows an explicit response pattern with its activity maximum at monetarily rewarded trials and no activity difference between all the trials leading to no material gain, irrespective of the performance level. This two step activity pattern, high in the MRO-high performance condition (MRO/GP) and significantly lower in all not extrinsically rewarded trials (MRO/PP; NMRO/GP; NMRO/PP) clearly indicates that in the present task setting dorsal caudate activity is elicited by experiencing extrinsic reward only and not by performance feedback. Hitherto, dorsal caudate activity has been linked to the processing of performance feedback and reward-related information (Elliott et al., 1997; Elliott et al., 2000; Delgado et al., 2000; Tricomi et al., 2006) and in monkeys also to anticipation of reward (Lauwereyns et al., 2002; Ding & Hikosaka, 2006). Delgado and colleagues (2004) found strong dorsal caudate activity in case of positive outcome linked to high incentive compared to no incentive (Delgado et al., 2004). They have suggested that dorsal caudate activity is influenced by incentive values. A similar finding is reported by Tricomi & Fiez, 2008. They have shown that the dorsal caudate is more robustly activated when feedback indicates task achievement and not simply a positive outcome and suggest that the dorsal caudate reflects the participants' goal and the personal value of this outcome. Our results support this finding in two ways. First, by showing that dorsal caudate activity is enhanced when achieving a personal goal (taking into account that subjects consisted of students, it may be speculated that to make as much money as possible is very likely a to be a goal) and second, by demonstrating that good performance is not enough to drive dorsal caudate activity.

Considering the differential implication of the dorsal caudate and putamen, it is questionable to sum these subcomponents to a functional superstructure. However, since the reaction pattern of dorsal putamen may merely reflect lacking statistical

power to differentiate between the different conditions or outcomes in the present experiment we have to leave it to future studies to further investigate the question of functional segregation of dorsal striatal structures.
Taken together, in contrast to the ventral striatum, dorsal caudate activity is driven by monetary reward. Positive outcome is not sufficient to activate dorsal striatum. The fact that ventral and dorsal striatum are involved in different processes, is also supported by clinical studies and the subcomponents of the striatum also differ in their anatomical and connectivity pattern (Haber & Fudge, 1997; Haber et al., 2000).
However, alternative interpretations of the absent interaction and main effect have to be discussed. Lack of significance may always be caused by a lack of statistical power. On the other hand it might also be argued, that dorsal caudate activity is influenced by the amount of feedback subjects are being given. In the reward trails (MRO/PP) subjects are presented not only the two dots along the line, as in all feedback, but additionally also the exact amount of money they are given. It might be argued that this more concrete feedback, allows them to better and more carefully evaluate their performance, which in turn could drive dorsal caudate activity.

A few interpretational aspects concerning our results have to be addressed. While it is surely valid to talk about intrinsic reward in the case of NMRO-trials, it has to be acknowledged that in the case of MRO-trials, additionally to the extrinsic reward experience, an intrinsic has to be assumed. It is possible that additionally to the monetary reward, subjects experienced an intrinsic pleasure of having performed well, However, it is very difficult to determine which parts of the subjects' motivation to perform well are intrinsic and which are not or to what degree the outcome is inducing an intrinsic and extrinsic reward experience (Frey & Jegen, 2001). So one has to keep in mind that whenever we talk about extrinsic reward, the subjects experience might be a mix of intrinsic and extrinsic nature.
Likewise, it has to be considered, that we did not measure "pure" intrinsic or "pure" extrinsic reward experiences. It is quite likely that the trials' outcomes are not evaluated independently but in relation to each other. This raises two issues that go hand in hand. One concerns the influence of extrinsic reward on the intrinsic reward experience and the other one concerns the potential occurrence of counterfactual reasoning. Counterfactual reasoning has been described as the ability to imagine alternative outcomes (Thompson & Byrne, 2002; Baird & Fugelsang, 2004; Byrne & Egan, 2004) and can take the form of the *if - then – simulation* heuristic as proposed by Kahneman and Tversky (1982). Counterfactual thinking enables the human to imagine past events or future outcomes, gives rise to emotions such as guilt, regret

or blame (Barbey et al., 2009). It cannot be excluded that in our experiment subjects engaged in counterfactual reasoning. It is likely that e.g. in a NMRO-trial when performance was well that subjects wished to be in a MRO-trial. The question arises if these processes may have influenced striatal activity and brought in an additional aspect, such as an additional cognitive and emotional evaluation of the outcome, that has to be considered. For the following reasons, however, we don't think that this was the case. First, in classical regret and counterfactual reasoning studies (Camille et al., 2004; Coricelli et al., 2005; Coricelli et al., 2007), there is a agency component, that "if only one had chosen differently, a better outcome would have been achieved". However in our task, subjects did lack the option to choose if they are in a MRO- or NMRO- trial and therefore lack the agency component. Instead, it was determined randomly before each trial, whether money could be gained or not. Therefore it seems unlikely that the potential wish to be in the other condition might influence our results in a manner comparable to counterfactual reasoning. Additionally, Coricelli and colleagues (2005) investigated the neural substrate of outcomes linked to agency (regret) and outcome linked to no sense of agency (disappointment). They found disappointment to correlate with neural activity in the temporal gyrus and the dorsal brainstem, while regret correlates with orbitofrontal activity. Even if subjects engaged in something like counterfactual reasoning (by wishing to have performed well in a MRO-trial) or experienced disappointment (by wishing to be in the other condition), based on current evidence this would not bias striatal activity.

The second issue concerns the influence of extrinsic reward on the intrinsic reward experience. The present study only permits speculation about the influence of monetary reward on intrinsic reward experience. To address this question, we are planning a future study that will measure two supplementary aspects that extend the current study. First, we will assess the experienced emotions and thoughts. Second, we will examine a separate group of subjects in the NR-condition, to avoid a bias of extrinsic reward on intrinsic reward experience. However, despite the remaining question marks, our data robustly show differential activity patterns for the dorsal and ventral striatum.

6.5.4 Conclusion

The aim of the present study was to investigate the effect of positive performance feedback and monetary reward on striatal activity. Ventral striatum activity is primarily influenced by positive performance, however, the significant interaction indicated that it's activity is also sensitive to the possibility of earning money. We argue that the

ventral striatum represents the total value of an outcome. The total value of an outcome may be influenced by the actual performance and the option of getting money. On the other hand, dorsal caudate activity is clearly driven by monetary performance. High performance only is not sufficient to drive enhance it's activity leve. The results suggest, that the ventral striatum and the dorsal striatum do not encode the same. Both, positive feedback about the own performance as well as monetary gain linked to the own performance may be rewarding. However, these two kinds of rewarding experience may be anchored differently in the human brain. While the rewarding value of money first has to be learned, the rewarding and motivating value of successful performance is already present in young infants (Kaplan & Oudeyer, 2007).

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7. General Discussion

The aim of this thesis was to investigate three aspects of feedback processing in sensorimotor transformation tasks and to reveal the underlying neural activity. These questions were addressed in three different studies using fMRI. The **first study** used a sensorimotor transformation task and investigated the influence of the spatial dimension of its sensory input and motor output signals. The **second study** aimed to identify the neural mechanisms of correct feedback versus incorrect feedback, that differed in magnitude. Finally, in the **third study** striatal effects of performance level and monetary gain were examined.

The findings of each individual study have been discussed in the specific discussion section. In the following, the findings are briefly summarized in the context of the respective research question as outlined in the introduction of the thesis. Furthermore, potential problems are discussed, thus resulting in an outlook towards potential future studies that elaborate on the work begun here.

7.1 Study 1

The aim of first study was to explore the role of the parietal cortex in processing spatial information, with respect to both sensory and motor signals. The central question was: **How is parietal cortex activity influenced by the analysis and transformation of visual stimuli that do or do not contain spatial information into motor responses that also do or do not contain spatial demands?** To address this question, we used a fully balanced 2x2 factorial design in which the spatial properties of sensory information as well as of motor responses were varied, thus resulting in four different task conditions.

A conjunction analysis revealed four clusters that were activated across all four trial types (i.e. they were active for high and low spatial demands with respect to sensory and motor processing). Two clusters were located in the frontal lobe (motor and prefrontal cortex) and the other two in the parietal lobe (IPS and Inferior parietal lobe). The inferior posterior parietal cortex (infPPC) and the intraparietal sulucs (IPS) are widely known to be involved in the analysis of spatial information in visual stimuli as well as in the planning of movements (Toni et al., 2001; Floyer-Lea & Matthew, 2004; Imamizu et al., 2001; Rizzolatti & Matelli, 2003).

As expected, IPS and infPPC were activated in all four task conditions. Importantly, however, the extent of the activations varied between the tasks. InfPPC and IPS

activation was lowest for isometric motor responses that are linked to a visual stimulus containing no spatial information, while somewhat greater activity was observed for isometric movement linked to spatially encoded sensory information. Greater increase in activity was associated with the two conditions involving dynamic movements.

Our analysis revealed that only a quarter of the IPS activity we found can be explained by the sensory stimuli while more than 50 % of the activity can be explained by the motor response. From this we conclude that motor response type has a greater impact on brain activity than does the type of visual stimulus.

Dynamic and isometric movements also differ in their impact on infPPC activity. Dynamic motor responses activate a large parieto-frontal network compared to the isometric motor response. This difference in activation may be attributed to the need for more coordination of muscle groups for dynamic compared with isometric movements. This increased demand on muscle coordination is most likely to rely on a more complex level of planning and programming. An increase in fronto-parietal network activity has also been reported with an increased complexity in motor movements (Wexler et al., 1997; Gordon et al., 1998; Harrington et al., 2000). Also behavioral data support the assumption that isometric and dynamic movement differ in complexity and programming demands. Significantly longer reaction times were shown for dynamic movements. These longer reaction times may be an indicator for these enhanced needs on programming.

One may question this statement by advancing that differences in RT could be due to factors other than planning, such as the execution of movement. To make sure the RT differences are not caused by low-level mechanical factors a control experiment was performed. Subjects had to manipulate the two tools upon a go-signal. Here, no discrete sensorimotor transformation had to be performed and the translations did not differ in difficulty. This experiment revealed comparable reaction time differences for both types of motor responses, so we conclude that reaction time differences could be attributed to unequal planning and motor demands from the two instruments.

Contrary to the large differences in activity extend and level, that were found between the two tools, only small differences were detected in the networks required to analyze the *visual stimuli*. Performing a spatial judgment of the visual stimuli vs. a color judgment in the context of visuomotor integration evoked activation differences only in supramarginal gyrus.

To find activity in the infPPC for spatial judgment is consistent with the dorsal stream

theory as proposed by Ungerleider and Mishkin (1982): This theory states that the dorsal stream is involved in the analysis of the spatial attributes of visual stimuli. Functional MRI studies have also consistently reported infPPC activation for spatial judgment tasks (Pinel et al., 2004; Kleinschmidt, 2004; Stephan et al., 2007). This indicates that the spatial analysis of visual information does not rely on a large network and recruits only little additional resources compared to the color judgment.

However, caution has to be applied and potential alternative explanations have to be considered. The two motor responses differ in the need for muscle coordination, they also differ in the effectors used, with the isometric task recruiting distal musculature and the dynamic task recruiting other, more proximal musculature. There are a number of potential factors in the dynamic vs. isometric contrast including spatial cues, muscle recruitment (isometric or dynamic), accuracy, timing, etc., which together have to be considered carefully when interpreting the activation differences.

A particular problem is that eye movement behavior may differ between the four paradigms. Eye movements are known to be processed in the IPS (Savaki et al., 2010, Konen & Kastner, 2008). Perhaps more eye movements are made in the dynamic than in the isometric task. This could also partly explain the differences in activity we find for the IPS.

Another difference between the two motor responses concerns the force needed for the manipulation and its possible impact in parietal activity. In order to control for the effect of force variability, a parametric analysis of BOLD responses was applied during the isometric handgrip condition, with force as a modulatory parameter. This analysis revealed only activation in the somatosensory cortex related to strength, as usually reported by force coding studies (Thickbroom et al., 1998; Cramer et al., 2002), but none in the parietal lobe.

Last we wanted to rule out any confounding effects for the visual stimuli with regard to their spatial properties. To ensure that colors are not represented in a spatially arranged continuum (e.g. light colors mentally represented on the left side and dark colors on the right side) an adjusted SNARC-paradigm was used (Dehaene et al., 1993). We found no systematic relation between color tone and RT, which indicates that colors are not mentally represented in a way containing spatial information.

7.2 Study 2

In the second study, the processing of errors caused by the agent and errors caused by environmental factors were investigated. The aim was to determine **the neural impact of these internal and external errors while at the same time investigating how error magnitude impacts brain activity.**

To investigate these factors, we asked subjects to perform a sensorimotor transformation task in which they were likely to commit motor errors (internal errors) of different magnitudes; in some trials they were given incorrect feedback (external errors) about their performance. Subjects were naïve to this additional manipulation.

Brain activity was established for three types of error information I) incorrect feedback about performance (non-motor external errors) II) the sum of the internal and external error (total error) and III) motor errors committed by the agent (*internal errors*).

For these three error types different areas were found to parametrically correlate with the magnitude of the error. The parametric analysis of ***external errors*** (i.e. errors induced by environmental factors) revealed activity in pMFC (BA 6/8), anterior insula, cerebellum, precuneus and IFG to correlate with the magnitude of *external errors*. Presumably, the anterior insula and the IFG activity reflect a negative emotional response evoked while facing unexpected and potentially unfair feedback (Lane et al., 1997; Buchel et al., 1999; Phelps et al., 2001; Phan et al., 2002; Phillips et al., 2003; Jabbi et al., 2008; Siegrist et al., 2005; Sanfey et al., 2003; Abler et al., 2005). The pMFC (BA 6/8) activity we found is in accordance with results obtained from error monitoring in cognitive tasks (Botvinick et al., 2001; Ullsperger & von Cramon, 2001; Fiehler et al., 2004; Holroyd et al., 2004; Ullsperger et al., 2007). In the incorrect feedback condition, feedback is distorted, and the outcome could therefore not be predicted correctly by the internal model. This could result in cerebellar and parietal activity.

The sum of these two error types (*internal and external errors*) activated partly overlapping but also distinct areas compared to external errors. We found that the activity of the MFG and the pMFC was enhanced with the magnitude of the *total error* fed back to the subject. This activity may mirror the need to update the motor response: the larger the errors were that subjects were confronted with, the higher the need to adjust behavior or an internal model relating action to expected outcome.

For the last type of error, the ***internal errors,*** no significant correlations with pMFC or any other hypothesized structures were found. The fact that pMFC correlates with *external errors* and with *total errors* but not with *internal errors* leads us to assume

that *internal motor errors* are processed differently from *external non-motor errors*. Our results suggest that detection of motor and non-motor errors apparently relies on different neural networks.

However, it is unexpected not to find pMFC activity to correlate with internal error size. Studies investigating error processing in cognitive tasks consistently report of pMFC activity (e.g. Carter et al., 1998; Botvinick et al., 2001; van Veen et al., 2004; Ullsperger et al., 2007). Our experimental task however, differs in one very important aspect from classical error-monitoring studies. The major task was to link variable positions of the target cue to a specific motor response. Obviously, cognitive error monitoring tasks also rely to a certain degree on sensorimotor transformation (e.g. correct → press index finger, incorrect → press middle finger), but they do focus on a cognitive evaluation of a stimulus (e.g. present or not, odd or even) too. Furthermore, failure in e.g. flanker tasks is mostly due to an incorrect evaluation of the presence or absence of a stimulus, and not due to an incorrect implementation of motor commands.

Another reason for this unexpected finding may be given by the theory of internal models (Kawato & Wolpert, 1998; Wolpert & Kawato, 1998). These internal models enable the agent to form a prediction about the sensory consequences of a motor action and to compare the predicted outcome with the actual outcome. When a movement is carried out, an efference copy of the associated motor commands is used to make a prediction of the sensory consequences of the movement. This sensory prediction can then be compared with the actual sensory feedback from movement.

However, several authors who have been investigating error monitoring and perception in cognitive tasks have pointed out that pMFC is only activated when a deviation from an expected target is detected (Knutson & Cooper 2005; Bubic et al., 2009). So it could be argued, that since the prediction of the sensory consequence of the motor command has already been made by the forward model, a deviation between target and feedback cue is not unexpected, and may therefore not trigger pMFC activity.

Evidence for this line of argument may be seen in the fact that pMFC activity was only detected in trials in which *external errors* were present or in which *external errors* had been added in addition to the internal errors– a component that could not have been predicted by the forward model. This argumentation may especially hold true in the case of the present study because subjects were acquainted with the tool before the fMRI session began, and had thus had the opportunity to develop a functioning internal model.

In general, in case of a motor error, three sources of failure are conceivable. The source of failure may lay in a faulty internal model. In this case the internal model has to be updated, which would entrain parietal and cerebellar activation (Blakemore, 2004). Assuming the internal model is correct, two additional sources can be assumed. The first one could be due to faulty programming. Assuming the programming is right, the second one could be due to a faulty translation of neural activity in the motor cortex to motor output on a muscular level. An interesting implication of the notion that the pMFC only codes unpredictable (external) errors would be that internal errors committed in our study are predominantly due to inaccuracies in motor programming or implementation rather than due to a prediction failure. The interesting question arises whether errors in the forward model can be distinguished from motor implementation errors and their detection. If we assume motor errors are caused by a faulty programming or implementation and not a faulty internal model, how come that we still find no pMFC activity to correlate with this unexpected outcome? Has the internal model already been informed about the unexpected outcome by afferent sensory signals and therefore cancelled out any unexpectedness? It would be very interesting to pursue this question further and carefully investigate the differences between faulty prediction and faulty implementation. However, the absence of an effect may be due to experimental factors such as the sample size or any nonlinearities in the BOLD response that are not accounted for in the regression model.

Another very important question however arises about the awareness of the source of errors. Our design did not allow to control for the awareness of the source of error and the attributional style of error source in every trial. In the post experimental questionaire 14 out 15 subjects explicitely reported to have had the impression that in some cases feedback was incorrect, but we cannot retrace in which trials they had this impression and what emotional and mental states were induced by incorrect feedback. However, we have strong support to assume that subjects were aware of the source of errors, at least for the larger deviations that involved additional external error. We found anterior insula to correlate with the external error size and anterior insular cortex has repeatedly been associated with being or become aware of facts (Ploran et al., 2000; Klein et al. 2008; Craig, 2009).

Last, I would like to encourage the attempt to unify the concept of internal models and error monitoring. The concept of internal models has so far been restricted to sensorimotor transformation tasks but it might be valuable to extend it to non-motor error perception. Especially since in the context of uncertainty, guessing or non-motor error perception per se cerebellar and parietal co-activation are often found

and in context of sensorimotor transformation tasks pMFC is reported too (Imamizu et al., 2004).

7.3 Study 3

The aim of the third study was to differentiate ventral and dorsal striatum activity according to their relative contribution to positive feedback and monetary reward processing. The research question was: **How does the ventral and dorsal striatum code positive feedback about good performance vs. the additional monetary reward?** To address this questions, we used a sensorimotor transformation task in which participants were monetarily rewarded for high performance in only half of the trials. Prior to each trial, subjects were informed whether their performance would be monetarily rewarded or not. Monetarily rewarding only half of the trials resulted in high performance trials, which were either monetarily rewarded and such that were not.

It is a very interesting result to find a distinct response pattern for the dorsal and ventral striatum. The activity level of the former seems only to be influenced by the reception of monetary reward. Performance feedback alone seems to play no role for dorsal striatum activation. On the other hand, ventral striatal activity is triggered by positive performance feedback, but also by reward. We find a significant interaction effect between these two components. T-tests show that the influence of positive feedback is dominant, whereas the monetary reward only has a minor additional influence. It has to be considered, that ventral striatum has been associated with many different stimuli that go beyond the classical definition of reward, such as money or positive feedback (Aron et al., 2004). Ventral striatal activity has been reported for tasks in which subjects had to rate the pleasantness of pictures (Kirk et al., 2009), the attractiveness of faces (Aharon et al., 2001) or were processing pleasant stimuli of erotic and romantic couples (Sabatinelli et al., 2007). In this context, it has repeatedly been suggested that the role of the ventral striatum should be viewed in terms of processing informationally salient events rather than specifically in terms of extrinsic reward (Horvitz, 2000; Zink et al., 2003; Zink et al., 2004; Phan et al., 2004). On the other hand, the dorsal striatum has been linked to the accomplishment of the task goal and not to positive feedback per se (Tricomi & Fiez, 2008). Our results support this view two-fold. First, by showing that good performance is not enough to drive dorsal caudate activity; and second by showing that dorsal caudate activity is enhanced when achieving a personal goal. Taking into

account that subjects consisted mostly of students, it may be speculated that to make as much money as possible is very likely to be a goal.

The differential activity pattern of the ventral and dorsal striatum indicates that these two kinds of rewarding experience (positive performance feedback and monetary reward) are encoded differently in the human brain. While the rewarding value of money first has to be learned (secondary reward), the rewarding and motivating value of "success" is already present in young infants (Kaplan & Oudeyer, 2007).

A very interesting question also concerns the potential impact of extrinsic reward and intrinsic reward experience or intrinsic motivation. In economics system there is the strong belief that extrinsic reward such as money has a positive impact on productivity. However, this skinnerian assumption has been questioned by psychologists since the early seventies (Deci, 1971; Kohn, 1993). It has been suggested that there is a hidden cost of reward (Frey, 2000) that could impair productivity, especially on a long-term perspective. Many experiments have suggested that extrinsic reward can, under certain circumstances, *undermine intrinsic reward mechanisms* and thus lead to a decrease in productivity or performance (Deci et al., 1999; Callan & Schweighofer; 2008). Extrinsic reward may have a crowding out effect on intrinsic motivation and may induce a shift from internal to external motivation.

In our study, we find no significant difference in performance between the two conditions. The question arises whether motivation was equal during rewarded and unrewarded trials and whether potential differences in motivation favored learning. Taking into account that the task was the same in both conditions and conditions were randomly swapped, we can exclude that subjects learned the task better in one condition than in the other. It is also conceivable that subjects may have considered the trials in which no money could be earned (regardless of the performance) as an exercise and applied their knowledge for the trials in which good performance resulted in monetary gain.

One last very important question concerns the emotional experience linked to the different outcomes. The first case concerns trials in which subjects performed poorly but could have won money if only they had been better. What emotions are induced by this feedback? Are subjects indifferent or do they get frustrated? Do they engage in some form of counterfactual reasoning? The second interesting case consists of the opposite constellation of trials, where subjects performed well but could not win any money. Different emotional and cognitive reactions are possible. Subjects caring about their own performance may experience "pleasure" or "satisfaction" about their

own performance, while subjects focusing on extrinsic reward may experience negative and frustrating emotions. Depending on the subjects' personality state (e.g. coping styles, locus of control) different reactions are to be expected (Kohn, 1993; Reitman, 1998; Deci et al., 1999). To answer these questions, a further study is needed in which the emotional states and the cognition linked to the feedback presentation are assessed.

7.4 Limitations and outlook

As in every experimental study, the question about the external and internal validity arises. All three experiments are based on a sensorimotor transformation task, in which several aspects were varied to investigate the different experimental questions. Thus, one can finally ask to which extent the task used in the experiments reflects a real-life feedback situation and whether results obtained in a standardized setting can be transferred to everyday human behavior.

Another issue concerns the method used. Our neuroscientific research method was fMRI, which is a very powerful and popular method to investigate brain activity. The advantages of fMRI are its noninvasiveness, high spatial resolution (compared to the electroencephalography, EEG) and ability to measure and locate activity of deep cortical structures like the striatum. On the other hand, its temporal resolution is rather poor. In this context, the processes of analyzing visual information, transforming them into a motor response and evaluating the feedback are fast processes. Unfortunately, the fMRI method is unable to disentangle processes at this time scale. The BOLD response between these single events is often highly intercorrelated and can therefore not be unambiguously attributed to either one of the underlying processes. EEG in turn could potentially shed light on these integration processes.

Based on the results acquired in this thesis, new questions arise. Does brain activity differ in time and amplitude if one has to process visual information containing spatial information vs. none? Does the transformation of visual stimuli differ in its neural demands depending on the modality it is transformed to (isometric or dynamic movements)? Can spectral differences be detected between trials in which money could be and trials in which no money could be won? Are motor errors already noticed by the internal models before the subjects are given visual feedback about their motor performance? Does the amplitude of event-related potentials correlate with the motor error? EEG could answer part of the abovementioned questions and complete our understanding of the functioning of the brain.

7.5 Conclusion

The aim of this thesis was to shed light on three different facets of feedback. We were able to show that different areas were activated, depending on the importance and meaning of the feedback – even though a very similar sensorimotor transformation task was involved in the three studies. This means that the different information contained in the feedback is analysed by the specialised areas in each case. Feedback processing is not a unitary construct. The different information contained in the feedback strongly modulates brain activity.

8. References

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